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**AN EXAMINATION OF
ADVERSE DRUG REACTION REPORTING TO
THE YELLOW CARD SCHEME**

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Doctor of Philosophy

ASTON UNIVERSITY

September 2007

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ASTON UNIVERSITY
**AN EXAMINATION OF ADVERSE DRUG REACTION REPORTING
TO THE YELLOW CARD SCHEME**

Anthony Richard Cox

Submitted for the Degree of Doctor of Philosophy, 2007

This thesis is an examination of the reporting of suspected adverse drug reactions (ADRs) to the UK's Yellow Card scheme, administered by the Medicines and Healthcare products Regulatory Agency (MHRA). The reporting of suspected ADRs to spontaneous reporting schemes, such as the Yellow Card scheme, is a major component of the post-marketing surveillance of pharmaceuticals. Under-reporting to such schemes is a major public health issue and the Yellow Card scheme has undergone several changes in the past ten years to respond to falling numbers of ADR reports.

Chief pharmacists in 209 hospitals were surveyed about ADR reporting schemes, the priority given to ADR reporting, and attitudes towards ADR reporting. ADR reporting had a low managerial priority. Local reporting schemes were found to be operating in 37% trusts, but there were few plans to start new schemes. Few problems were discovered by the introduction of pharmacist ADR reporting. Chief pharmacists had concerns about the competence of hospital pharmacists to detect ADRs and were in favour of increased training. Lack of time on wards, and recruitment difficulties were suggested as reasons for hospital pharmacist under-reporting. Teaching hospitals appeared to have an increased interest in ADR reporting.

Heads of pharmacy and medical schools in the UK were surveyed about the teaching of ADRs at undergraduate level. The Yellow Card scheme was included in course material and in course assessments at the majority of institutions. There was support for the supply of further educational material and specialist speakers on ADRs from the MHRA.

A retrospective analysis of reporting trends within the West Midlands region from 1994, showed increasing or stable reporting rates for most sectors of reporters, except for general practitioners (GPs). The West Midlands region maintained higher ADR reporting rates, than the rest of the UK. National reporting figures showed a worrying decline in ADR reports from healthcare professionals. Variation was found in the ADR reporting rates of Acute NHS Hospital Trusts and Primary Care Trusts (PCTs) in the West Midlands region, including correlations with prescribing rates and other PCT characteristics.

Qualitative research into attitudes of GPs towards the Yellow Card scheme was undertaken. A series of qualitative interviews with GPs discovered barriers and positive motivators for their involvement in the Yellow Card scheme. A grounded theory of GP involvement in the Yellow Card scheme was developed to explain GP behaviour, and which could be used to inform potential solutions to halt declining rates of reporting.

Under-reporting of ADRs continues to be a major concern to those who administer spontaneous reporting schemes. This study has explored the management of ADR reporting in the hospital sector, the teaching of undergraduates about ADR reporting, the underlying trends in reporting, and examined in depth the interaction of GPs with the Yellow Card scheme. Policy recommendations have been suggested.

Keywords: adverse drug reaction reporting, spontaneous reporting, pharmacovigilance, general practitioners, pharmacists

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Dedication

To my wife, Dianne, and children, Lauren and James, who have supported me throughout this research.

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Abbreviations used within this thesis:

ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
BPS	British Pharmacological Society
CHM	Commission on Human Medicines
CPT	Clinical Pharmacology and Therapeutics
CSD	Committee on Safety of Drugs
CSM	Committee on Safety of Medicines
DAP	Drug Analysis Printout
FDA	Food and Drug Administration
GMC	General Medical Council
GP	General Practitioner
MCA	Medicines Control Agency
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	National Institute for Health and Clinical Excellence
OTC	Over-the-counter
PCT	Primary Care Trust
RPSGB	Royal Pharmaceutical Society of Great Britain

Chapter 1 Introduction and background

1.1. Introduction to this thesis

“No drug which is pharmacologically effective is entirely without hazard. The hazard may be insignificant or may be acceptable in relation to the drug’s therapeutic actions. Further not all hazards can be known before a drug is marketed; neither tests in animals nor clinical trials will always reveal all the possible side effects of a drug. These may be only known when the drug has been administered to large numbers of patients over considerable periods of time”

Committee on the Safety of Drugs, Annual report 1969-70.

The development of modern medicines has led to major reductions in human suffering. However, history shows that the use of medicinal substances is not without risk¹. The unintended adverse consequences of drugs continue to be a major public health issue, and their detection, measurement and management is of major interest to health professionals, governmental regulatory agencies, the pharmaceutical industry and the public. Health professional engagement with spontaneous reporting schemes, such as the UK’s Yellow Card scheme is therefore a key area of interest for those involved in drug safety monitoring.

This thesis explores the current state of adverse drug reaction (ADR) reporting within the UK, by focusing on several contemporary areas of concern.

The first part of the present study had the aim of examining the current role of hospital pharmacist involvement in the Yellow Card scheme. In 1997 hospital pharmacists were accepted as formal reporters to the Yellow Card scheme. As hospital pharmacists generally operate within the constraints of a departmental structure, it was decided to survey the views chief pharmacists held, the extent of local ADR reporting schemes, any problems that hospital pharmacist reporting had caused, and the interest medicines management devices, such as Drug and Therapeutic Committees, had in ADR reporting.

A second area of interest was undergraduate education. Education about ADRs and ADR reporting systems has previously found to be of importance to attitudes towards reporting

ADRs. Concerns about undergraduate medical education has also been recently expressed in a number of publications. A survey of heads of medical and pharmacy schools was undertaken to ascertain extent of inclusion of the Yellow Card scheme within course material and assessments.

The third area examined was trends in ADR reporting within the West Midlands, the United Kingdom as a whole, and differences in reporting between various professional groups and NHS institutions. Data was obtained from the West Midland Yellow Card Centre and the Medicines and Healthcare products Regulatory Agency (MHRA). The examination of such trends was important to be able to direct resources at areas of concern.

The final area of research was a qualitative study of GPs attitudes and interactions with the Yellow Card scheme. GP ADR reporting is in decline, however, there is little information to explain what changes are causing this change in behaviour. The aim of this study was examine the beliefs, attitudes and knowledge of GPs, and to develop a grounded theory of GP involvement with the Yellow Card scheme.

The remainder of this chapter will describe what ADRs are, how they are classified, give a brief history of ADRs, describe the incidence of ADRs, and describe the purpose, history, and operation of spontaneous ADR reporting schemes with particular reference to the UK's Yellow Card scheme run by the MHRA.

1.2. *Adverse drug reactions*

1.2.1. What is an adverse drug reaction?

All medicines with the ability to produce a therapeutic effect also have the potential to cause unwanted adverse effects. For the purposes of drug safety, having clear definitions of what constitutes an ADR is important. In 1972 the World Health Organisation (WHO) technical report defined an ADR as:

*“a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function”.*²

The use of the phrase “at doses normally used in man” is important because it distinguishes the effects of noxious effects of drugs caused during normal use of the drug from toxic effects caused from poisoning³. It should also be noted that the WHO definition makes no reference to any pharmacological link between the ADR and the drug. In that case, the term “side effect” has been used:

*“Any unintended effect of a pharmaceutical product occurring at doses used in humans, which is related to the pharmacological properties of the drug.”*⁴

However, in practice the terms “side effect” and ADR have been used interchangeable within both the published literature and by clinicians. Most notably, in the UK the British National Formulary (BNF) continues to use the term “side effect” in drug monographs, rather than ADR⁵. The use of the term “side effect” has been discouraged by some authors in an attempt to reduce confusion in drug safety terminology⁶ and by those who note the term “side effect” is ambiguous since it does not exclude unexpected benefits of treatment⁷. The term ADR is also preferable to the “toxic effect”, which is only applied to exaggerations of the desired therapeutics not seen when normal doses of the drug concerned are used³.

Edwards and Aronson⁷ reviewed definitions of ADRs, and viewed existing definitions as deficient. The WHO definition was considered vague; the term noxious being considered highly subjective. The threshold of what is considered noxious may also change, dependent on the benefit the drug provides, or the severity of the disease process it is being used to treat. The WHO definition also excluded the potential for contamination of a product, ADRs that included an element of error, and ADRs to excipients in a medication (which are not the active drug). The reference to the term “drug” also excluded the use of herbal treatments.

In an attempt to overcome these points, Edwards and Aronson⁷ proposed the following definition of an ADR:

“A appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regime, or withdrawal of the product.”

The term adverse effect or adverse reaction can be used interchangeable; adverse reaction pertaining to the point of view of the patient and adverse effect applying to view from the perspective of the drug.

Another definition used includes the technical definition used by the European Commission⁸, who define an ADR as:

A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.[...]

Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (according to the ICH E2A Guideline this means that a causal relationship cannot be ruled out).

Adverse reaction also includes adverse clinical consequences associated with use of the product outside the terms of the Summary of Product Characteristics or other conditions laid down for the marketing and use of the product (including prescribed doses higher than those recommended, overdoses or abuse).

The notion of a suspicion of a causal relationship between the drug and the adverse effect is central to the definition of an ADR. Confusion sometimes occurs within the literature when the term adverse drug event (ADE) is used. An ADR to a drug is an adverse outcome in a patient that is attributed to an action of a drug, whereas an ADE is an adverse outcome in a patient, which occurs after the use of a drug, but which may or may not be linked to use of the drug³. It therefore follows that all ADRs are ADEs, but that not all ADEs will be ADRs.

This distinction is important in the assessment of the drug safety literature, since the term ADE can be used when it is not possible to suggest a causal link between a drug treatment and an adverse outcome. In the context of reporting ADRs to regulatory agencies, such as the

MHRA Yellow Card scheme, the term suspected ADR or reportable ADR are commonly used.

1.2.2. The classification of adverse drug reactions

Several attempts have been made to create classification systems for ADRs. These classifications can be used both for educational purposes, clarifying thinking on how to avoid and treat ADRs, as well as helping those who work within a regulatory environment.

One of the most common classifications systems is the Rawlins system of classification⁹, which divides ADRs into two main groups: Type A and Type B (See Table 1-1).

Table 1-1 : The Rawlins classification of adverse drug reactions

Type A reactions	Type B reactions
Augmented pharmacological effect	Bizarre effects apparently not related to pharmacology
Predictable effect	Unpredictable
Dose-dependent	Not dose dependent
High morbidity	Low morbidity
Low mortality	High mortality
e.g. bradycardia associated with a beta-adrenergic receptor antagonist	e.g. anaphylaxis associated with a penicillin antibiotic

Rawlins described Type A reactions as the normal, but quantitatively abnormal, pharmacological effects of a drug. This could include the primary pharmacological effect of the drug, as well as any secondary pharmacological effects of the drug, e.g. the anti-cholinergic activity of tricyclic anti-depressants. Type A reactions occur in individuals lying at the extremes of dose-response curves for pharmacological effects, so those could include those who develop toxicity, as well as those who experience a therapeutic failure – which has been argued to be an ADR¹⁰. Type A reactions are more common, accounting for 80% of reactions¹¹.

Type B reactions are qualitatively abnormal effects, which appear unrelated to the drug's normal pharmacology, such as hepatotoxicity from isoniazid. They are more serious in nature, more likely to cause deaths, and are often not discovered until after a drug has been marketed¹².

The Rawlins classification has undergone further elaboration over the years (Table 1-2), to take account of ADRs that do not fit within the existing classifications, leading to the creation of a number of other types of reactions⁷:

Table 1-2 : Additions to the Rawlins classification of adverse drug reactions

Type of reaction	Features	Examples
Type C: Dose-related and time related	Uncommon Related to the cumulative dose	Hypothalamic-pituitary-adrenal axis suppression by corticosteroids
Type D: Time-related	Uncommon Usually dose-related Occurs or becomes apparent some time after use of the drug	Carcinogenesis
Type E: Withdrawal	Uncommon Occurs soon after withdrawal of the drug	Opiate withdrawal syndrome
Type F: Unexpected failure of therapy	Common Dose-related Often cause by drug interactions	Failure of oral contraceptive in presence of enzyme inducer

More recently, the DoTs system of classification has been developed by Aronson and Ferner¹³. Noting that the current classification was defined only by the properties of the drug, such as its known pharmacology and the dose dependency of its effects, the authors created a classification to take into account the properties of the reaction, and the properties of the individual. They proposed a three dimensional classification based on dose relatedness,

timing and patient susceptibility (DoTs), which they considered would improve both drug development and patient care. The DoTS classification has been proposed for use in pharmacovigilance planning¹⁴.

Although the Rawlins classification has its deficiencies, it is still widely referred to within the literature. It is arguable that it is a simple classification system to use when teaching healthcare professionals about ADR reporting.

1.2.3. A brief history of adverse drug reactions

Public concerns about ADRs are usually based upon the most recent drug controversies, however it is important to note that the issue of drug-related medical harm has been a longstanding concern. The euphoric effects of the poppy were recorded in ancient Sumeria in 4000 BC, and tachycardia caused by a herbal preparation containing ephedrine was recorded in China in 2000BC¹⁵. Drug interactions, and their potential to cause harm, were noted by Homer in 950BC, who said: *"Many drugs were excellent when mingled and many were fatal"*. The oath of Hippocrates included the statement: *"I will neither give a deadly drug to anybody if asked for it nor will I make a suggestion to that effect."*¹

One of the first attempts to fully describe the adverse effects of a medicine was William Withering's account of digitalis, published in 1785, which still provides a meticulous description of the adverse effects of digitalis¹⁶.

The introduction of chloroform in 1831, also led to one of the first systematic attempts to assess the safety of a medicinal product. After a number of sudden deaths upon induction of anaesthesia with chloroform, the British Medical Association and *The Lancet* undertook one of the first collaborative investigations to examine the safety of a drug¹⁷. The final report published in 1893 concluded that chloroform depressed respiration and had deleterious cardiac effects – including cardiac arrest¹⁵.

In 1937, The S.E. Massengill Company, in the USA, developed a liquid preparation of sulfanilamide. The raspberry-tasting pink medicine contained 72% diethylene glycol, which had documented toxicity. Over a four week period after distribution of the drug in September of 1937, 353 patients received the elixir, 30% of whom died – including 34 children¹⁸. The deaths were attributed to the diethylene glycol, and the tragedy was responsible for the successful passage of the 1938 Federal Food, Drug, and Cosmetic Act which was the first legislation to demand evidence of safety before a drug was marketed.

Sadly, episodes of diethylene glycol poisoning continued to occur throughout the 20th century in nations such as Nigeria, India, Argentina, and Haiti^{19,20}. In 2006, cough medicines made using diethylene glycol contaminated glycerin, sourced from China, were responsible for the suspected deaths of over 300 people in Panama²¹.

Vaccines have also been the cause of major safety disasters, On April 12th, 1955 Jonas Salk's polio vaccine was licensed in the United States and production licences granted to five pharmaceutical companies. Over a period of ten days 380,000 doses were administered – mostly to healthy young children. Within two weeks, five cases of children experiencing post-vaccination paralysis in the vaccinated arm, were reported to regulatory authorities. Each child had been vaccinated by one particular firm's vaccine: Cutter Laboratories.

Investigation showed that cell debris contained in Cutter's vaccine had led to failure of formaldehyde to inactivate virus particles, leading to the distribution of 120,000 doses of live poliovirus. Forty thousand children developed polio, 51 were permanently paralysed, and 5 died. The incident was also responsible for a further polio outbreak that paralysed a further 113 people and killed a further 5 people. The Cutter Incident was one of the worst pharmaceutical disasters to occur in the United States²².

However, it was the thalidomide disaster that captured public attention and ensured that major regulatory changes in drug safety would occur throughout the world, including the UK. Paradoxically, thalidomide was initially introduced and marketed to address a serious safety concern. In the 1950s barbiturates were in widespread use. However, the toxic dose for barbiturates in children is very small, and accidental poisonings were a noted problem.

Thalidomide was serendipitously discovered in 1954, by a small German family firm called Chemie Grünenthal, while trying to develop new antibiotics. Chemie Grünenthal (motto “We must succeed at any cost”) already had a record of rushing drugs to market and associated drug withdrawals due to safety concerns²³. After finding no beneficial effects in animal studies, they examined thalidomide use in epilepsy. No anti-epileptic activity was found, but many patients experienced a profound deep sleep and found that thalidomide produced a calming and soothing effect.

On October 1st 1957 thalidomide was marketed as the sedative Contergan in Germany. Unambiguous claims of safety led to its sale as an OTC product in Germany. A large marketing campaign, involving 50 medical journals, 50,000 therapeutic circulars and 250,000 individual letters to doctors was launched. Emphasising safety, the message was distributed that thalidomide was safe, even if used in suicide attempts. The company cited as evidence of safety in promotional material accidental overdoses of thalidomide in children.

Distillers Ltd, a UK whiskey producer who had become involved in penicillin production during World War II, sent their chief medical advisor to Germany with a view to marketing thalidomide in the UK. He returned saying, *"If all the details of this are true, then it is a most remarkable drug. In short, it is impossible to give a toxic dose."* Distillers marketed thalidomide in the UK as Distaval in April of 1958, and placed a similar emphasis on the safety of thalidomide in promotional material(Figure 1-1).

Figure 1-1 : Distiller's advertisement for thalidomide (Distaval)



In August of 1958, Chemie Grünenthal declared the drug was suitable for use in pregnant and nursing mothers, an indication Distillers added with no supporting evidence. By 1959 Chemie Grünenthal had received reports peripheral neuritis associated with thalidomide, though they publicly denied that such reports existed. The drug continued to be marketed as a safe drug.

In 1961, an Australian doctor called Jim McBride²⁴ and a German doctor Dr Widukund Lenz²⁵ independently made the connection between thalidomide and birth defects. Even after Chemie Grünenthal were made aware of the possible connection, they posted 70,000 promotional leaflets to German doctors stating "*Contergan is a safe drug*". Thalidomide was eventually withdrawn in December 1961 leaving between 8,000 and 12,000 deformed children in its wake.

Like the Massengill Elixir tragedy before it, the thalidomide disaster had a major effect on the regulation of medicines, but this time the effect was worldwide. Between 1961 and 1965

Australia, Canada, Czecholovakia, Ireland, the Netherlands, New Zealand, Sweden, the UK, the US and West Germany all established spontaneous reporting systems for suspected ADRs²⁶. The key principles of modern day pharmacovigilance systems were established. In 1968 ten countries agreed to pool all reports sent to national monitoring centres into a central database, as part of a WHO-sponsored collaboration. In the UK it led to the enactment of the Medicines Act 1968 giving the government power to license pharmaceutical companies, and individual products and clinical trials. It also established the Medicines Commission and the Committee on the Safety of Medicines (CSM), to advise the Government on the exercise of their new powers. The spontaneous reporting system established by the CSM was the Yellow Card scheme²⁷.

The 1970s saw another unexpected and serious adverse reaction. The development of the beta-adrenergic receptor blocking agents by James Black's ICI team was widely seen as a breakthrough in drug development, however the introduction of this class of drugs had the seeds of the next major drug tragedy within it. Pronethalol, the first ever beta-adrenergic receptor blocker produced by ICI, was not without problems. It was found to cause cancer of the thymus gland in mice and was restricted to use in those patients whose lives were seriously at risk²⁸. In 1964, it was replaced by a safer analogue: propranolol. Further pressure to produce a cardioselective beta-adrenergic receptor blocker led to the launch of practolol in June 1970, licensed for use in asthmatic patients.

Initially only a few reports of rashes were received by the CSM. In April 1972, the CSM drew ICI's attention to a small number of patients with a more severe form of rash. In May of 1974, two dermatologists wrote to the British Medical Journal noting that they were seeing rashes resembling psoriasis associated with the use of practolol²⁹. A week later Peter Wright, an eye surgeon, wrote to the CSM informing them of his soon to be published paper about a group of patients with psoriasis-like rashes linked to dry eyes – including irreversible

scarring of the cornea³⁰. Before the publication of these letters in the BMJ, only a single report of conjunctivitis and four reports of psoriasis had been received.³¹

With this increased publicity, doctors made the connection between the drug and patient symptoms. An additional 90 reports of eye damage, ranging from dryness to corneal ulceration, and blindness were received. The number of cases of psoriasis was raised from 11 to 49, and 4 cases of sclerosing peritonitis were reported – a particularly dangerous bowel condition that could have fatal results³². Sclerosing peritonitis was often delayed for two or more years, often appearing after the patient stopped the drug. Half the reports to practolol occurred after the drug had been withdrawn. Between the 1st of July 1963 and the 31st of December 1975, the year practolol was withdrawn, 2014 reactions were reported, including 91 cases of sclerosing peritonitis, of which 15 were fatal. By 2005 the total number of cases of sclerosing peritonitis had risen to 201, including 22 fatal cases³³.

In the UK, practolol had remained on the market for four years. Over 100,000 people had been treated, with hundreds seriously affected. Practolol had been used widely in several countries before the risk of oculomucocutaneous syndrome had been noted. Wasn't this exactly the sort of problem spontaneous reporting scheme set-up in the wake of the thalidomide disaster had been meant to detect? The incident of minor eye complaints in clinical trials was 14%, compared to 6% before use of the drug³⁴. Early recognition of these milder symptoms could have led to early diagnosis and prevention of some of the worse cases of eye damage.

In the 1980s the drug benoxaprofen (Opren), a non-steroidal anti-inflammatory agent (NSAID), was marketed as having potential benefits over other NSAIDs in rheumatoid arthritis. In April and May 1982, a small number of cases of jaundice in elderly patients appeared in the medical press. The liver disease was thought to be due to a build up of the drug in the body, particularly in the elderly with impaired renal excretion of the drug. A

company offer to include a warning about dose reduction in the elderly or sick patients, was turned down by the CSM, who withdrew the drug in August 1982. Despite this the CSM were blamed for delaying the withdrawal of the drug and inadequacy of their monitoring arrangements. Severe criticism was given in a two-part television investigation called "*The Opren Scandal*" broadcast in January 1983³⁵.

The withdrawal of benoxaprofen was not universally welcomed. The FDA received hundreds of letters from doctors and patients asking if benoxaprofen would still be available to them³⁵. Dennis Potter, the famous playwright, complained that he had been left "*high and dry*"³⁶. A similar example of patient pressure to keep a drug on the market was seen with the withdrawal of alosetron in 2000, a drug treatment for irritable bowel syndrome, which was associated with severe ADRs such as ischaemic colitis and death. The FDA and GlaxoSmithKline were inundated with thousands of letters from patients to keep the drug on the market³⁷. The drug was made available again under a risk management programme run by GlaxoSmithKline in 2002.

Not all drug safety issues are related to real effects, and one of the most taxing drug safety issues in the UK in recent years has been concerned with the safety of the MMR vaccine. The publication in 1998 of a paper by Andrew Wakefield and co-authors³⁸, and a subsequent controversial press conference at which Wakefield called for suspension of the triple MMR vaccine³⁹, led to a crisis in confidence about MMR vaccine which had a detrimental effect on vaccination rates⁴⁰. The 1998 paper was retracted by ten of the authors in 2004⁴¹, and the editor of the Lancet stated the publication of the paper would have been handled differently if the full context in which the research had been done had been known⁴². The alleged link between MMR vaccine has been refuted by both epidemiological studies^{43,44} and virological studies^{45,46}.

The introduction of the COX-II selective NSAIDs, celecoxib (1998) and rofecoxib (1999), was seen as an improvement in safety due to a theoretical reduction in gastrointestinal ADRs. The VIGOR trial, comparing rofecoxib to naproxen, did appear to reduce gastrointestinal toxicity⁴⁷. However, there was an apparent excess of myocardial infarctions in the rofecoxib group, which was initially ascribed to cardio-protective effects of naproxen. In May of 2000, the Netherlands Pharmacovigilance Center detected a cardiovascular signal for rofecoxib⁴⁸. However, this signal was not widely disseminated, and similar safety signals were not picked up by other spontaneous reporting systems. As late as 2005, there were no recorded case reports of cardiovascular events following the use of rofecoxib in peer-reviewed journals.

Although regulatory agencies did improve warnings to health professionals about the use of COX-II inhibitors in at risk groups, the association of cardiovascular events with COX-II inhibitors was still attributed to the use of a drug in an elderly patient group and the potential of comparator drugs to have an anti-thrombotic effects.

In September of 2004, an interim safety analysis of a study of rofecoxib evaluating its use in the prevention of colorectal cancer (APPROVe) noted that the rofecoxib arm of the study was associated with a significantly increased risk of cardiovascular events⁴⁹. The trial was terminated and rofecoxib was withdrawn from the market on September 30th. Combined interim analysis of two trials of celecoxib (the APC trial⁵⁰ and the PreSap trial⁵¹) showed an increase dose-related risk of cardiovascular events⁵². Both trials were terminated.

An editorial in JAMA by Topol⁵³ argued that the sudden fall of a class of drugs into disrepute after association with a cardiovascular hazard highlighted major concerns about drug safety systems. In the US aggressive marketing had produced high usage of a class of drugs, before long-term safety had been established. Drazen⁵⁴ argued that the spontaneous reporting systems that operated well at finding rare events (such as liver failure or rhabdomyolysis), were unable to detect an increased incidence of a common event, such as a stroke or heart

attack. This was especially true in a population that already had a relatively high background risk of such events, such as rheumatoid arthritis patients. Minor changes in incidence levels of such events, could have major effects in a large exposed population. Graham et al⁵⁵ suggested that the 106.7 million prescriptions for rofecoxib dispensed in the USA were responsible for an estimated 88,000 to 140,000 excess cases of serious coronary events, 44% of which may have been fatal.

1.3. The incidence and burden of adverse drug reactions

The burden of ADRs on healthcare systems is considerable. A 1998 meta-analysis⁵⁶ estimated that ADRs were ranked between the fourth and fifth leading cause of death in the US in 1994 (106,000 deaths, 95% CI, 76,000-137,000). However, there is wide variation in the published studies looking at the incidence of ADRs, in terms of populations and detection methods. It is clear that there is no shortage of ADRs for health professionals to report to regulatory agencies.

1.3.1. ADRs as cause of admission to hospital

The involvement of drugs in the admission of patients to hospital has been studied in a variety of healthcare systems⁵⁷⁻⁷⁵. A meta-analysis by Lazarou et al⁵⁶, found that the incidence of serious ADRs upon admission to hospital was 4.7%, with 0.13% being fatal.

Wiffen et al⁷⁶, in a systematic review of ADRs in hospital patients, found an ADR admission rate in Europe and the UK of 7%.

A 2004 prospective analysis in two UK hospitals found 1225 admissions out of 18,820 admissions (6.5%)⁷⁷. In 80% of the cases the ADR was the primary cause of admission. The overall fatality rate was 0.15%. This large, well-conducted study is the most reliable data for drug-related admissions in the UK at present. The authors calculated that the projected annual

cost of ADRs to the NHS was £466 million, equivalent to seven 800 bed hospitals being occupied by patients.

1.3.2. ADRs that occur during hospital treatment

A number of studies have examined ADRs occurring in hospital inpatients⁷⁸⁻⁸⁸. Krähenbühl-Melcher et al⁸⁹ reviewed original publications on drug-related problems in hospitalised patients published between 1990 and 2005. Unfortunately, due to some studies not differentiating between ADRs and ADEs, both terms were combined into ADEs. An average of 6.75% of patients experienced an ADE. The frequency of ADEs detected by spontaneous reporting (2.1%) was lower than that from patient monitoring (11%). Drug interactions were responsible for 17% of all ADEs.

Lazarou et al's 1998 meta-analysis showed an in-patient ADR incidence of 2.1%, with 0.19% incidence of fatal ADRs⁵⁶. Wiffen et al⁷⁶, found an inpatient rate of 7.3% for European and UK studies.

1.3.3. ADRs that occur in primary care

Less reliable information is available about the incidence of ADRs in UK primary care. A two-year prospective study undertaken in a part urban, part rural general practice asked all patients given a drug for the first time to complete a questionnaire⁹⁰. Patients were asked to describe in their own words if they had experienced any symptoms that they felt were related to the use of the drug and were followed up in an additional consultation. From 807 patients, 41% of patients felt they had "certainly" or "probably" had a reaction to the drug prescribed. Most of the suspected ADRs were minor and self-limiting in nature, such as nausea, diarrhoea, or dizziness.

Mulroy⁹¹ surveyed the extent of iatrogenic disease in patients in a mixed rural and industrial practice, consisting of 6,200 patients over a sample month. Out of 9,315 consultations, it was found that 239 (2.6%) were thought to be due to ADRs (81%) or surgical treatments (19%).

Although the study gave a definition of iatrogenic disease “*Any adverse reaction to medication undesired or unintended by the physician*”, there was no description of the methods employed to detect the iatrogenic disease during the consultation perhaps accounting for the difference in incidence with Martys study. Both Mulroy and Martys’ studies were limited; only examining the incidence in the practice they worked within.

Kelleher and Carmichael⁹² reported in a very small study of one months duration that reportable ADRs were detected in 1 in every 90 consultations.

Millar⁹³ examined the incidence of consultations due to ADRs in a rural practice in Scotland. All doctors within the practice were asked to record any ADRs occurring over a six month period. During the study 272 ADRs were reported out of 16,253 consultations (1.7%), although a retrospective validation of the study found that there was an under-reporting rate of 27%. Although there was no analysis of how many ADRs were serious in nature, three of the patients had to attend hospital. Fifty percent of ADRs were accounted for by three groups of drugs (antidepressants, antibiotics, and NSAIDs).

US studies of outpatient and ambulatory care patients have shown rates of ADRs/ADEs between 2.8% and 21%⁹⁴⁻⁹⁷.

1.4. The importance of post-marketing surveillance and pharmacovigilance

The inherent weaknesses of pre-marketing studies, mean that post-marketing surveillance of medicines is essential to detect previously un-noticed adverse effects of treatment. The science of this process is called pharmacovigilance and has been defined as “*the study of the safety of marketed drugs under the practical conditions of clinical use in large communities*”⁹⁸.

The importance of rapid detection of potential safety signals is highlighted by the fact that an examination of 5 drugs withdrawn from the US market, revealed that 19.8 million people (10% of the US population) were exposed before withdrawal⁹⁹.

1.4.1. Weaknesses of clinical trials

Only common, usually pharmacologically predictable, reactions are detected by clinical trials due to their relatively small statistical power, which can detect efficacy, but not rare effects. Mathematically it can be calculated that if n patients are treated with a medicine, and none suffer a particular ADR, then the incidence of that ADR will be 95% likely to lie between $0/n$ and $3/n$ ¹⁰⁰. New medicines have on average only been used in trials involving 1500-2500 patients^{101,102}. This could mean that as many as 1 in 833 patients could suffer a previously unknown adverse effect of a new medicine. Even if a trial included 10,000 patients and 10,000 controls, it would still only detect, with 95% confidence, ADRs with an incidence of less than 1 in 3333. Pre-marketing trials do not have the power to detect important reactions that occur at rates of 1 in 10,000, or fewer, drug exposures. Clinical trials also fail to detect ADRs temporally separated in time.

Clinical trials do provide an essential role in assessing the more common ADRs that may occur with use of a drug, and the use of a control group provides clearer causation than observational studies, as demonstrated by the case of the COX-II inhibitors excess cardiovascular risk⁵⁰⁻⁵². However, the quality and quantity of safety reporting in published trials is poor¹⁰³, with many trials using more space to list authors names than safety results. Also initial drug dosages can be too high, with 21% of initial licensed dosages being reduced - in 70% of cases because of safety concerns¹⁰⁴.

1.4.2. The value of case reports

As seen by the case of thalidomide²⁴ and practolol³⁰, astute and vigilant clinicians submitting case reports to the medical press has been of importance in drugs safety. Some have argued

that many case reports “*cry wolf*”, however Leiper argued that since 35 out of 47 case reports in one study had been subsequently confirmed as ADRs, that they had a remarkable success rate[Leiper, #7]. Despite case reports being viewed as one of the weakest forms of evidence, Aronson and Hauben^{105,106} have made a strong argument they can provide definitive information not provided by other sources.

Case reports have been described as a form of non-systematic voluntary reporting¹⁰⁷. However, reports are not solicited and their appearance in the medical literature is in the gift of medical editors. Case reports take time to be published, and their production is time consuming. Editors may demand a causal link, or a case series, requiring higher standards of investigation than regulatory agencies demand from a spontaneous report. These high standards can prevent case stories, and deter many clinicians.

1.4.3. Spontaneous reporting

Existing spontaneous reporting systems of pharmacovigilance rely on professional suspicion of a causal link between a drug and an adverse event. In contrast to case reports, they are a form of systematic voluntary reporting, which promote the formal reporting of suspected ADRs to a regulatory body.

Spontaneous reporting has a number of advantages. It is relatively cheap to administer, and can follow a product throughout its life. It can also accept reports to over-the-counter medication and herbal treatments¹⁰⁸.

Spontaneous reporting schemes are passive surveillance systems; reliance is placed on the ability of health professionals to recognise possible ADRs and to distinguish these from symptoms related to the underlying disease. With regard to quantifying the risk, such systems supply a numerator (the number of reports) but estimates of the incidence of reactions cannot be made, because the measure of the population exposed cannot be ascertained accurately.

The MHRA estimates that about 40% of the safety signals investigated by the Agency are generated from spontaneous reports¹⁰⁹. Despite calls for improved pharmacoepidemiological studies in the wake of the withdrawal of benoxaprofen¹¹⁰, and more recently after concern about cardiac events associated with rosiglitazone¹¹¹, spontaneous reporting will remain important for the detection of rare events¹¹². The spontaneous reporting of suspected ADRs to regulatory authorities continues to be of major importance in detecting potential safety signals. An analysis of 21 drugs withdrawn in France between 1998 and 2004 showed that 19 withdrawals were linked to spontaneous case reports¹¹³. A similar analysis of 11 product withdrawals between 1999 and 2001 in the UK and US showed evidence from spontaneous reports supported the withdrawal of 8 products¹¹⁴. Spontaneous reporting has also been shown to be superior to Phase IV post-marketing studies¹¹⁵. Rawlins' argued that both the medical and lay press had over-emphasised the limitations of spontaneous reporting, creating a popular mythology that spontaneous reporting schemes did not identify new ADRs¹¹⁶.

In some cases the lack of availability of higher standards of evidence may mean that case reports from spontaneous reporting schemes may be of high importance. For example, in the detection of ocular adverse reactions to systemic medications, spontaneous reports to regulatory bodies, case reports, and the US National Registry of Drug-induced ocular side effects have been essential to detect important ADRs¹¹⁷.

1.4.4. Signal detection

It is beyond the scope of this thesis to go into great depth on the subject of signal generation, but an appreciation of the methods employed is useful, in order to understand some of issues relating to the reporting of ADRs by health care professionals. Signal detection is covered in more detail elsewhere¹¹⁸⁻¹²⁰.

A signal can be described as a possible causal relationship between an adverse event and a drug, which was previously unknown. Others have also extended the method to detect drug-drug interactions¹²¹ and even potential benefits of drugs¹²².

The nature of the spontaneous reporting data collected and its method of collection makes the direct application of probabilistic statistics to spontaneous reporting limited¹²³. Data acquired by monitoring schemes are from individuals who have already made a judgement about the involvement of the drug, and are unlikely to have reported unless they felt the events were connected. In addition, reports have been obtained by a varied set of people with differing levels of competence, training, experience and awareness¹²³. Reporting is biased, with a tendency for reporting rates to be higher with newly introduced drugs. Media stories, regulatory action and even legal cases¹²⁴ can provoke reporting of particular reactions. Crucially, spontaneous reporting databases cannot give estimates of the incidence of ADRs.

Despite calls for improved reporting rates in order that spontaneous reporting databases reflect the true incidence of ADRs, this is an unattainable ideal. In fact, the detection of signals is possible even with the well-documented levels of under-reporting¹²⁵.

One useful analogy for signal detection in a spontaneous reporting database is to think of a radio signal, which is disguised by the background radio “noise”¹²⁶. Statistical methods of signal generation can be thought of as methods of tuning in to capture the radio signal from the background noise.

Statistical approaches scan the data for drug-adverse event pairs that are strikingly “out of kilter” with the database as a whole¹²³. Only rarely will a signal provide such strong evidence that a restriction on use of the drug or its withdrawal is immediately required¹²³. A signal could be due to causes other than the drug, such as confounding factors, such as particular groups of patients being “channelled” into receiving the drug. For that reason, the strength of

the signal also depends on the strength of the spontaneous reports^{127,128}. Early methods of detecting signals by looking at trends within the data were rudimentary in nature. The Canadian regulatory agency placed individual reaction cards into “alerting pigeonholes”¹²⁹. A rapidly filling pigeonhole was indicative of a potential safety issue.

A statistical method developed by the MHRA is the use of Proportional Reporting Ratios¹³⁰. The proportion of all reactions to a drug is compared to the same proportion for all drugs in the database by use of a 2x2 table. The null hypothesis is that the proportions of the chosen drug are the same as the proportion for the whole database.

Such calculations can be run automatically by modern computer systems, providing the opportunity to scan large databases for potential signals of new ADRs. However, while these mathematical approaches do develop hypotheses and give the illusion of an objective estimate of risk, they are not conclusive in themselves¹³¹. Individual analysis of cases is still required.

An important observation about signal generation is that in order to find serious ADRs, a certain level of background “noise” is required¹³². If only serious and unexpected reactions are reported, then only the more serious and unexpected will eventually stand out. There is therefore a benefit to spontaneous reporting schemes receiving reports that supply “ordinary” ADRs, to serve as background data¹³².

1.4.5. International collaboration

The need for international collaboration was seen early in the development of spontaneous reporting systems. A scientific group met in March 1963 shortly after the thalidomide disaster¹⁵ to examine the benefits of co-operation on ADR monitoring. A WHO Pilot research Project was established in Alexandria, Virginia USA in 1968, with help from the US government¹²³. The centre moved to Geneva in 1970, and then in 1972 to Sweden, where it is currently known as the Uppsala Monitoring Centre. In 2007, the centre was receiving

200,000 spontaneous reports a year from 78 countries²⁶. The WHO centre has had considerable success in developing new methods of computer based signal generation using Bayesian probability neural networks¹³³, which had become essential given the large size of their database (3.5 million cases).

1.4.6. Under-reporting to spontaneous reporting schemes

Under-reporting is of considerable importance to spontaneous reporting systems such as the Yellow Card scheme. Under-reporting reduces the sensitivity of reporting systems to potential drug safety issues delaying identification of new ADRs, leads to underestimates of the importance of problems, and is open to selective reporting which may introduce serious bias²⁶. Under-reporting to The Yellow Card scheme was noted early in the scheme's life. In 1966, despite the possible relationship between oral contraceptives and thrombosis being constantly in the public eye, and requests for doctors to be vigilant for these reactions, an examination of 53 women known to be taking the oral contraceptive who had died from thromboembolism, showed that only 8 cases (15%) had been reported to the Yellow Card scheme¹³⁴.

Under-reporting has been demonstrated in hospitals. Smith et Al¹³⁵ looked at 20,065 consecutive acute general admissions in the UK. Over three years from April 1990 to March 1993, they found 1,420 reports of suspected ADRs, of which a third (477) met MHRA guidelines for submission of a Yellow Card. However, only 30 (6.3%) were sent. The majority of non-reported reactions were well-known reactions to established drugs related to the admission of the patient (74.8%), ten of which were due to black triangle drugs. The main reason for under-reporting was suggested to be that serious well-known reactions to established drugs causing admission to hospital were not considered reportable.

Similar under-reporting is seen in general practice. A study of GP reporting examined reporting by 100 doctors based within 24 practices¹³⁶. During the 36,470 consultations

monitored over a six-week period, 633 (1.7%) contained a suspected adverse drug reaction. Of these reactions 37 met the MHRA's reporting criteria (0.1% of the observed reactions), but only 5 were reported (13.5% of these cards). This percentage is relatively high compared to other under-reporting studies, which could be explained by GP awareness, since the study design meant that GPs were aware of the fact ADRs were being examined. When extrapolated to the total number of GP consultations in that year and compared to GP reports received by the CSM in 1982, it was calculated that less than 5% of reportable reactions occurring in GP practice were being reported. Kelleher and Carmichael in a very small study in the West Midlands reported a reporting rate of 30%, although this study's methods were limited and the rate may have been influenced by the involvement of a CSM regional monitoring centre⁹².

Martin et al¹³⁷ examined 10 black triangle drugs used in 2034 patients in data obtained from Prescription-event Monitoring studies. Of 3045 recorded ADRs found, 275 (9%) has been reported to the Yellow Card scheme, with the highest reporting rates in the serious unlabelled reactions(32%). The lowest reporting rate was seen for non-serious listed ADRs (6.5%). The reporting of serious labelled ADRs was only slightly greater than that of non-serious labelled reactions.

Dent et al¹³⁸ examined emergency admissions with an International Classification Disease (ICD) related to warfarin toxicity (Y442) and those submitted to the Yellow Card scheme from the same hospital over a 12 month period. Out of 25,679 emergency admissions 18 cases were assigned a code related to warfarin toxicity. During the same period 5 reports were made to the Yellow Card scheme concerning warfarin. Only one case was found by both methods, showing that considerable under-reporting for serious reactions to established drugs is occurring. An examination of Swedish reporting rates has also shown that serious ADRs of a transient nature (such as anaphylaxis) were less likely to be reported to

regulators¹³⁹. In another comparison of ICD-10 coding with spontaneous reporting, Cox et al¹⁴⁰ found 49 of 21,365 patient episodes coded as ADRs over a four month period, of which 33 were reportable ADRs to the Yellow Card scheme. None had been reported to the Yellow Card scheme.

Hazell and Shakir¹²⁵ performed a rigorous systematic review of the under-reporting of ADRs. In total they found 37 studies using a variety of methods to estimate the level of under-reporting. The median level of reporting across all the studies was 6% (interquartile range 2%-18%). They found no evidence of differences in reporting rates between GPs and hospital doctors overall, although national differences in ADR reporting cultures may be present. There was some evidence of selective reporting, with GPs studies indicating an increased tendency to report serious ADRs, which other studies have found^{137,141}. There was evidence of considerable under-reporting of serious, and even fatal, ADRs in a hospital setting.

As already noted, under-reporting of suspected ADRs is not confined to the UK. Examination of under-reporting to a Spanish Regional Pharmacovigilance system showed an overall reporting rate of 5%, and showed that under-reporting was greater for psychiatric and gastrointestinal reactions¹⁴². Severe effects were reported more than moderate effects and the reporting rate was higher for recently marketed drugs, showing that reporters positively select cases. The reporting rate to the French pharmacovigilance system has been reported as 5%¹⁴³.

Problems related to under-reporting of events to outside agencies by healthcare professionals are not confined to ADRs. Recently, the House of Commons Committee of Public Accounts expressed concern that only 4% of GPs report untoward events and clinical incidents to the National Patient Safety Agency (NPSA)¹⁴⁴. Notifiable diseases, such as tuberculosis, are also under-reported^{145,146}, despite the fact that in the UK it is a legal obligation, attracts a fee, and diseases often have confirmatory lab results proving causality that suspected ADRs generally lack.

1.4.7. Causality assessment of suspected ADRs

The assessment of whether a drug is responsible for a suspected ADR is of great importance in both the regulatory environment and within the pharmaceutical industry. Reporters to spontaneous reporting schemes are requested to submit suspected ADRs, and such reports have variable levels of information upon them. For example, since rechallenge with the suspected drug is often ethically unacceptable¹⁴⁷, very few reports contain such information.

In spontaneous reporting the generation of a signal of an adverse event is caused by the accumulation of reported cases of the event in a database, however the strength of the individual cases reported may influence the decision making process. A number of cases with near certain probability of a link to the drug and a low background incidence of the particular reaction may be enough to trigger regulatory action, whilst a series of more improbable cases of a reaction which has a high background incidence may not raise suspicions. For example, a number of reports of cardiovascular events (common in the general population) to a drug used in individuals with risk factors for cardiovascular events, such as non-insulin-dependent diabetics, might not stand out from the general database. However, often causality is difficult to conclusively prove in pharmacovigilance and a high degree of suspicion may be all that is necessary for regulatory action¹⁴⁸.

One of the most common methods of causality assessment in use is unstructured clinical assessment, also known as global introspection¹⁴⁹. Expert review of clinical information is undertaken and a judgement is made about the likelihood of the reaction being due to drug exposure. The assessment of complex situations, often with missing information, is open to variation between different assessors, and this has been one of the criticisms of global introspection. Studies have shown marked disagreements between experts¹⁵⁰. Despite these concerns, the WHO international monitoring centre uses global introspection for case assessment¹⁴⁹, assigning standardised causality categories to suspected ADRs¹⁵¹ (Table 1-3).

Table 1-3 : WHO Uppsala Monitoring Centre causality categories

Category	Description
Certain	Pharmacologically definitive, with rechallenge if necessary
Probably/likely	Reasonable temporal relationship, unlikely to be attributed to disease processes or other drugs, with reasonable dechallenge response
Possible	Reasonable temporal relationship, but could be explained by concurrent disease or drugs. No information on withdrawal
Unlikely	Temporal relationship improbable, concurrent disease or drugs provide plausible explanation
Conditional/Unclassified	An event which requires more data for assessment
Unassessable/unclassifiable	An event that cannot be judged because of insufficient/ contradictory information which cannot be supplemented or verified

In order to address some of the criticisms of global introspection, a number of alternative methods of assessing causality have been developed using standardised decision algorithms, which are considered by some to be more objective and less susceptible to assessor bias. One of the most commonly used algorithms used to assess causality is the Naranjo algorithm¹⁵². Using a questionnaire points are added or taken away based on the responses to a series of questions, such as *“Did the adverse reaction reappear when the drug was re-administered?”*. The total score is then used to place the assessed reaction on a scale of definite, probable, possible, and doubtful. Algorithms also give different results in comparison to global introspection and may be less open to the effects of confounding variables, such as underlying disease states or concomitant drugs¹⁵³. However, even the use of an algorithm does not avoid assessor variability¹⁵⁴.

A third method of causality assessment involves the application of Bayesian probability theory. This assesses the probability of an event occurring in the presence of a drug (the posterior probability) given the prior probability of that event occurring without the drug, and the evidence from clinical trial data, epidemiological data and components of the specific case, such as history, timing, rechallenge and any other factors in the case¹⁴⁹.

Outside of the pharmacovigilance environment in companies and regulatory agencies, the informal assessment of causality by healthcare professionals is also important. The raising of suspicion in the mind of a reporter of a connection between the exposure to a drug and an adverse event is an essential step, before consideration of whether or not to report a suspected ADR can be undertaken. Although, such assessments may lack the formality of expert or algorithmic assessment, they are likely to take into account similar factors. A list of such factors is set out in Table 1-4, which is based upon work by Shakir¹⁵⁵.

Table 1-4 : Factors that may raise or suppress suspicions of a drug-induced event

<p>The temporal relationship between the exposure to the drug and the subsequent event.</p> <p>The clinical and pathological characteristics of the event – events which are known to be related to drug use, rather than disease processes</p> <p>The pharmacological plausibility – based on the observer's knowledge of pharmacology</p> <p>Existing information in published drug information sources – whether or not the event has been noted by others</p> <p>Concomitant medication – which may be considered the cause of an event</p> <p>Underlying and concurrent illnesses – may alter the event or be considered the cause of the event</p> <p>Dechallenge – disappearance of symptoms after dose reduction or cessation of therapy.</p> <p>Rechallenge – reappearance of symptoms after dose increases or recommencement of therapy</p> <p>Patient characteristics and previous medical history – past history of the patient may colour the view of the event</p> <p>The potential for drug interactions</p>

1.5. The UK's Yellow Card Scheme

In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) performs the executive function of the Licensing Authority responsible for medicines for human use. The MHRA is advised on matters of human medicinal substances by the Commission on Human Medicines (CHM), who also have a remit *“to promote collection and investigation of information relating to adverse reactions for human reactions for the purposes of enabling such advice to be given.”* Therefore the Yellow Card scheme is jointly administered by the MHRA and the CHM.

1.5.1. History of the Yellow Card scheme

The Yellow Card scheme was not the first spontaneous reporting scheme for ADRs in the UK. In 1960 an ADR registry was set up by the *Royal College of General Practitioners*¹⁵. Over a four-year period it collected 75 reports, although the scheme was only publicised to the membership of the college.

In August 1962, in the wake of the thalidomide scandal a sub-committee of the standing Medical Advisory Committee to the Minister of Health was set up. Its report *“Safety of Drugs”*, published in 1963, advised the establishment of a Committee on Safety of Drugs (CSD) and advised that new drugs should be subject before marketing to adequate toxicity testing in animals and clinical trials in man. It also advised on the establishment of a central registry for suspected ADRs found after marketing. The CSD was established a few weeks later under the chairmanship of Sir Derrick Dunlop, and held its first meeting on June the 6th 1963.

By the February 1964 the CSD had issued its first drug safety alert, in consultation with manufacturers, drawing attention to the adverse effects of monoamine oxidase inhibitors, and their potential adverse interaction with tyramine containing products such as cheese. Notably,

setting an example for some later drug withdrawals, this action was condemned by psychiatrists concerned that it would lead to drugs being withheld from patients.

By April of 1964 the CSD central registry was ready to start. The Royal College of General Practitioner's scheme was subsumed into the central registry, which became the Yellow Card scheme. The CSD consulted with British Medical Association (BMA), who agreed on the likely benefit of the scheme, with caveats about reports to the scheme not being made available as legal evidence. Sir Derrick Dunlop wrote to all doctors on the 4th May 1964 asking them to report all unexpected and severe reactions suspected to be related to drugs and all reactions to new drugs. Four key principle of the scheme were established at this point²⁷:

- Suspected adverse reactions should be reported; reporters do not need to be certain or prove that the drug caused the reaction.
- It is the responsibility of all doctors and dentists to report.
- Reporters should report without delay.
- Reports could be made, and would be treated, in confidence.

Confidentiality was recognised as an important issue; Dunlop's original letter stating that: *"all reports or replies that the committee receive from doctors will be treated with complete professional confidence by the committee and their staff. The health ministers have given an undertaking that the information supplied will never be used for disciplinary purposes or for inquiries about prescribing costs."*¹⁵⁶

By the end of 1964 the professional staff of the CSD comprised of three members of the medical profession and 2 pharmacists¹⁰⁷. Early operation of the scheme asked for simple reports, supplying prepaid postcards on Yellow Card. Follow-up was obtained by the use of medical field-workers visiting reporters when further information was needed. It was policy to acknowledge every report, and from 1969 a summary of all reports to the suspected drug

was supplied to reporters¹⁵. GPs were the main contributors in the early days, with disappointing levels of reporting from hospital doctors.

No attempt was made by the CSM to lay down precise definitions of terms such as new, serious or unexpected. Initial Yellow Cards contained no instructions for reporters, or information about the indication being treated.

One of first successes of the Yellow Card scheme was benziodarone (Cardivix), a coronary vasodilator¹⁵. In the spring of 1964 the CSD received 11 reports of jaundice, with 1 dead and 2 seriously ill. Benziodarone had been on the market since 1962, but had been promoted to GPs during February 1964. The use of the drug was not considered high, suggesting that the jaundice was occurring commonly. CSD field workers followed up reports, discovering the reaction occurred between 8 and 16 weeks after the administration of the drug. The drug was withdrawn by the manufacturer in co-operation with the CSD, who publicised the case in the British Medical Journal¹⁵⁷.

In 1971 the CSD was changed to the Committee on Safety of Medicines (CSM); the use of the term “drugs” being considered too emotive¹³⁴.

Reporting levels remained very stable, but in 1976 there was a profound and apparently consistent increase in the rate of reporting. Possible factors included concern about new drugs in the wake of the practolol incident, the introduction of the *Current Problems* series of drug safety articles by the CSM, and the placing reminders into GP prescription pads¹⁵⁸.

After the withdrawal of benoxaprofen in 1982, the CSM set-up the Graham-Smith Working party on ADRs to address under-reporting to the Yellow Card scheme, which suggested that increased availability of cards should be a priority¹⁵⁹, as well as increased publicity of the Yellow Card scheme¹⁷. A symbol was introduced to draw attention to drug under intensive surveillance, an inverted triangle ‘▼’. This was originally a red triangle, but pharmaceutical

industry opposition pressure led to the 'black triangle'³⁶. 1986 saw another step rise in reporting, thought to be due to the placement of reporting forms into the BNF and GP prescription pads¹⁵⁸.

By 1989 the Yellow Card scheme had received over 200,000 reports and was receiving nearly 20,000 reports annually. Yellow Cards were widely available in prescription pads, the British National Formulary, the Monthly Index of Medical Specialities (MIMS) and the ABPI datasheet compendium. Sixty percent of reports were coming from general practitioners, 20 percent from hospital doctors and 20 percent from industry¹⁶⁰. In 1990 the BMJ included a copy of a revised Yellow Card.

On the 1st of April 2003 the MCA was merged with the Medical Devices Agency (MDA) and the Medicines and Healthcare products Regulatory Agency (MHRA). On the 30th of November 2005, the CSM was replaced by The Commission on Human Medicines (CHM). The Yellow Card scheme continues to be administered by the CHM and MHRA.

The Yellow Card scheme has continued to be responsible for the detection of drug safety signals. A number of successes of the yellow card scheme are listed in Table 1-5.

Table 1-5 : Selected successes of the Yellow Card scheme²⁷

Year	Medicine	Safety issue	Regulatory action
1995	Tramadol	Psychiatric reactions	Warnings
1995	Cyproterone acetate	Dose-related hepatotoxicity	Monitoring requirements and restricted indications
1995	Quinolone antibiotics	Tendonitis, tendon rupture	Improved warnings
1996	Alendronate	Severe oesophageal reactions	Warnings and revised dosing instructions
1998	Isotretinoin	Psychiatric reactions	Improved warnings
1999	Aristolochia	Renal failure	Banned
2000	Cisapride	Serious cardiovascular reactions	Suspended
2001	Bupropion	Seizures	Improved warnings
2002	Olanzapine	Hyperglycaemia, diabetes and exacerbation of diabetes	Monitoring recommendations and improved warnings

During the past ten years ADR reporting has been extended to hospital pharmacists in 1997, community pharmacists in 1999, and nurses in 2002. This is in part a reaction to falling numbers of ADRs from a 1992 peak in reporting¹⁷. In recent years, the level of GP reporting has become of concern¹⁶¹.

1.5.2. Current operation of the Yellow Card scheme

Reports to the Yellow Card Scheme are made on yellow reporting forms available in the BNF, MIMS, from the regional Yellow Card Centres (YCCs) and direct from the MHRA via a free phone number. Reports can also be submitted electronically at <http://www.yellowcard.gov.uk>.

Over the years the reporting card has been redesigned as the level of information required has changed. In 2000, a revision of the General Medical Council's guidelines on confidentiality led to the anonymisation of the Yellow Card Scheme¹⁵⁶. Reporters are advised only to provide a local identification number, initials and the patient's age, rather than a patient's name, date of birth or NHS number. A copy of the current Yellow Card is in Figure 1-2..

Figure 1-2 : The current MHRA Yellow Card



1.5.3. The reporting criteria of the Yellow Card scheme

The current reporting criteria of the Yellow Card scheme are:

Any suspected reaction, to the following groups of agents, should be reported, no matter how trivial:

Drugs and vaccines that are being closely monitored (indicated by a black triangle '▼' in the British National Formulary);

Any drug used in a child;

Any herbal preparation.

For established products, any suspected serious reactions should be reported. Serious reactions include those that are fatal, life-threatening, disabling, incapacitating or which result in or prolong hospitalisation and/or are medically significant.

Congenital abnormalities following drug use are also classified as serious.

1.5.4. How the Yellow Card scheme operates

Statistical methods for detecting signals of ADRs in a database of spontaneously collected reports have been described earlier, but it is important to note that the Yellow Card scheme is only one of many methods used by the MHRA to identify safety issues.

Data from over half a million Yellow Card reports is held in an MHRA information management system called Sentinel. The combination of patient-anonymous reports and an increase in the size and professions of the reporter base means that duplicate reports are possible, and potentially more difficult to discover. The Sentinel system is able to identify duplicate reports and pools the information from multiple reports of the same reaction.

A crucial part of the any reporting scheme is the classification of adverse reactions within the database. The MHRA use the Medical Dictionary for Regulatory Activities (MedDRA); a

structured dictionary of medical terms adopted as an international standard by the International Conference on Harmonisation¹⁶².

1.5.5. Strengths and weaknesses of the Yellow Card Scheme

Spontaneous ADR reporting systems such as the Yellow card scheme are regarded as the classic drug safety alert ('signalling') system and their major purpose is to provide early warnings of possible hazards from use of medicines. Such systems are relatively cheap to operate and provide continuous safety monitoring throughout the lifespan of a medicinal product and the major strength, limitations, and operation have already been described. However, one of the strengths of the Yellow Card scheme has been its ability to obtain reports directly from healthcare professions, rather than pharmaceutical companies. In other systems, such as the American MedWatch Scheme, the majority of reports are received through pharmaceutical companies¹⁶³.

The scheme also examines the use of drugs in a large and varied population with regard to sex, disease states and concomitant medication, which enables the MHRA to obtain information about factors which may pre-dispose patients to ADRs. This was demonstrated by the use of Yellow Card data to discover the increased risk of extrapyramidal ADRs in children and women¹⁶⁴.

1.5.5.1. Internet reporting.

The lack of availability of Yellow Cards has been cited as a reason for not reporting. As computers become more widely used in the healthcare environment, electronic reporting may become a useful method of capturing formerly unreported reactions. The MHRA has established the website <http://www.yellowcard.gov.uk>, which provides an online ADR submission form and guidance on reporting.

As far back as 1985 electronic reporting of ADRs was seen as a way of reducing the delays between the suspicion of an ADR and its reporting to the regulator, and reduce work for the

regulator. In 1985 a pilot scheme of computer terminals was posited as the possible start of a widespread switch to reporting electronically compared to the use of paper work – although it was slightly more complex and lengthy than the Yellow Card¹⁶⁵.

1.5.5.2. Should ADR reporting be made a legal requirement?

Reporting to the UK Yellow Card scheme is a voluntary activity. In some countries, such as Sweden, the reporting of ADRs to their equivalent scheme is a legal requirement. However, reporting rates to the UK's Yellow Card scheme are higher than those in countries with a legal obligation. Medical confidentiality also means that enforcement of such a law is practically impossible. The independent review of the Yellow Card scheme did not endorse payments for reporting and there is currently no UK government interest in changing the voluntary nature of the scheme¹⁵⁶.

1.5.5.3. Dissemination of drug safety information from the Yellow Card scheme.

The MHRA is under a legal obligation to provide information to manufacturers of medicinal products. Companies are provided with restricted access to anonymous data about their products. All reporters to the Yellow Card scheme receive an acknowledgement of their report. When filling in their Yellow Card reporters have the option of ticking a box for further information. If ticked they will be sent a Drug Analysis Print (DAP) of reactions within the Sentinel database to the suspected drug. A DAP lists all reactions reported to have occurred in association with the named suspect drug. Since a Yellow Card report may contain more than one reaction, the DAP will contain more reactions than Yellow Card reports. Data are included for the multi-constituent products as well as single products. ADRs are listed in a hierarchical structure based upon the MedDRA dictionary¹⁶². The date of the earliest reaction is listed, as well as the date when the data was extracted.

There are some important guidance points, made available by the MHRA, about the interpretation of the DAPs:

- Reports are suspected reactions, not proven reactions. The listing of a reaction with a drug does not in itself provide evidence of causality.
- Medicines are commonly used in combination. For example many vaccines are used in combination. It can be difficult to ascribe a suspected reaction to an individual vaccine or drug.
- Certain conditions can occur spontaneously without a drug being administered. If a drug is used in a large population there may be co-incidental temporal relationships leading to an ADR report.
- The reactions do not give a basis for determining the incidence of any reaction. The exact number of reactions is unknown due to under-reporting, and the total number of patients using the drug is not known.
- Numerical comparisons cannot be made between different drugs, on the basis of a DAP report. Comparisons are misleading since they do not take account of the variations in ADR reporting, the extent of the use of a drug and other confounding variables such as the channelling of high-risk patients towards drugs perceived as safer than others.

The MHRA has also found safety bulletins an extremely useful tool, if well distributed. In the past doctors, dentists, coroners, and pharmacists received *Current Problems in Pharmacovigilance* published by the now defunct CSM. This bulletin published the outcomes of regulatory decisions, advice to prescribers and new safety concerns. Some of these safety messages are also found in the relevant sections of the BNF. The increase in the reporter base (in particular the admission of a large number of nurse reporters) has led to some discussion about additional and more effective methods of dissemination of safety messages. *Current Problems in Pharmacovigilance* used to be published three to four times a year, but from 2004 to 2006 only two editions were published. In August 2007 the MHRA replaced *Current Problems in Pharmacovigilance* with a monthly electronic publication entitled *Drug Safety Update*. The journal is intended for all UK healthcare professionals, and is provided in electronic form only at the MHRA website (<http://www.mhra.gov.uk>).

Other publications by the MHRA include '*Dear Doctor/health professional letters*' which are cascaded throughout the healthcare system to highlight important safety issues that require urgent attention.

The MHRA website is an increasingly important aid in distributing drug safety information. As well as publishing electronic versions of the MHRA information about drug safety issues, and general information about the MHRA and CSM, the MHRA website has a rolling front page that carries recent news and link to other relevant sites.

1.5.6. The Independent Review of Access to the Yellow Card Scheme

In April of 2004 *An Independent Review of the Yellow Card Scheme* was published¹⁵⁶. The report was published on the fortieth anniversary of the scheme, and was highly supportive of the original principles of the Yellow Card scheme.

The primary purpose of the review was to identify the conditions under which whole data from the individual Yellow Card scheme might be released, give the increased pressure from external researchers and the pharmaceutical industry for greater access to the Yellow Card database. Although it was expected that most requests would be for subsets of the data, others might wish to have access to the entire database for signal detection methods. A major concern was that such data could be misinterpreted if the limitations of the data were not recognised, and false conclusions might be reached about safety, and adverse effects on public health. However, given the prime purpose of the Yellow Card database is the detection of important drug safety signals, it was considered unethical not to allow greater access. Refusal could also be seen as being obstructive and against the interests of drug safety.

As well as the dangers of misinterpretation and misunderstanding from independent analyses, concern was expressed by some groups during the consultation period that the Yellow Card data may be used for purposes not expressed when the scheme was founded. However, there

was wide support for optimising the use of the Yellow Card data for research and public health, so long as it did not deter reporting. It was also considered essential that patients should have the confidence that their identity and personal data would not be disclosed for research purposes without consent.

The review divided the data into three categories:

Set I: Aggregated anonymous-identifiable data excluding all patient and reporter details

Set II: Information held within individual Yellow Cards, excluding patient and reporter identifiable data.

Set III: Information from the Yellow Card, with an opportunity for obtaining further information from the reporter.

It was recommended that Category I data should be published regularly on the MHRA website. The frequency of publication was not specified, but the committee suggested that the rate at which the data profile changes and the observation that frequent feedback improves reporting of ADRs should be borne in mind. The committee felt that publishing all aggregated and unidentifiable Yellow Card scheme for all drugs in the UK would be an “enormous task”. Currently, the MHRA have a selection of DAPS available on their website for download, along with advice on interpretation of the material. Aggregated anonymous-identifiable data not provided on the website, is available on request under the Freedom of Information Act.

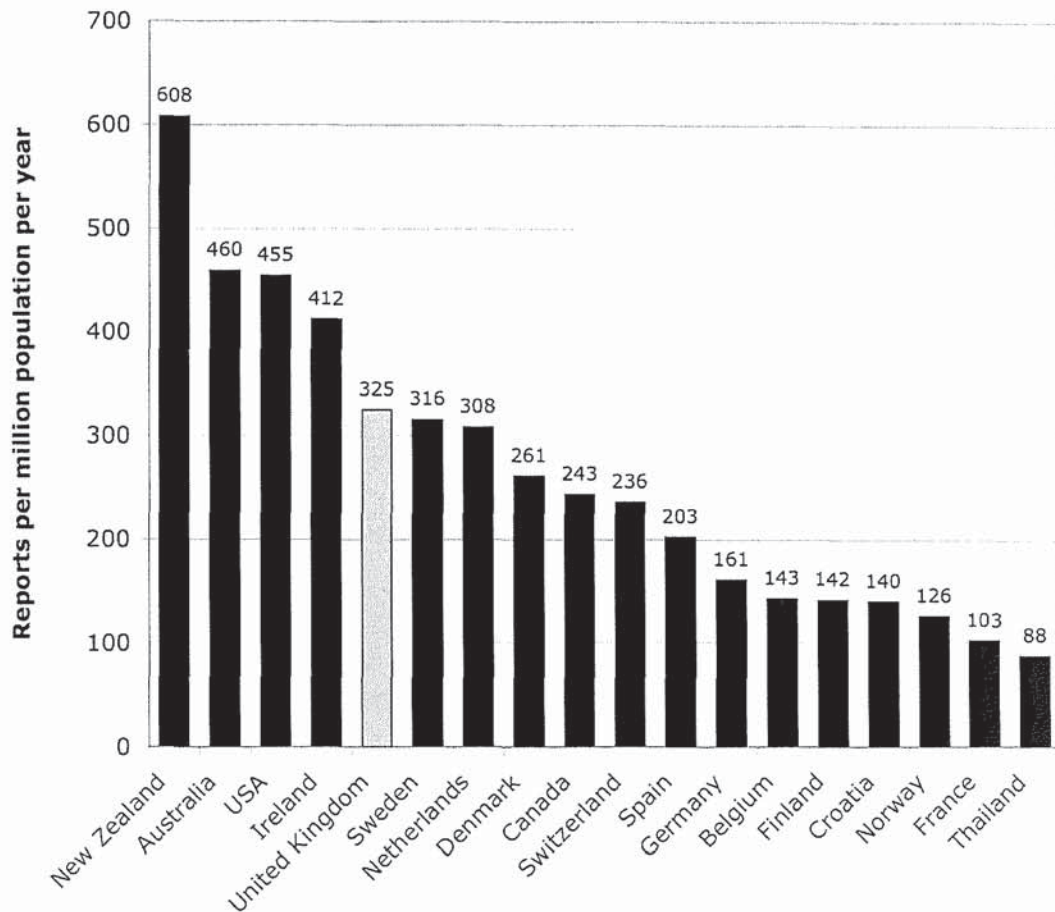
1.5.7. External views of the Yellow Card scheme

The Yellow Card scheme has in recent years come under scrutiny from the National Audit Office (NAO)¹⁶⁶, the Public Accounts Committee of Parliament¹⁶⁷, and more recently the *Independent Review on Access to the Yellow Card Scheme*¹⁵⁶. Although all have recognised the valuable contribution the MHRA has made to public health, some points were made about the operation of the Yellow Card scheme.

The NAO suggested that the MHRA should build on its existing regional networks and work with others such as hospital and community pharmacists and consultants, in order to aid the dissemination of key information on medicines safety to health professionals. The public accounts committee noted that efforts to improve reporting rates were seen to have met limited success. The committee also found that the MHRA had a narrow view of its public role and no public profile. Even amongst doctors, there was limited awareness of its role. The MHRA was asked to look at the possibilities of patient reporting; *The Independent Review on Access to the Yellow Card Scheme*¹⁵⁶ also supported this view advising that patients should be allowed to directly report to the Yellow Card scheme.

Despite criticism for under-reporting, the UK's spontaneous database is internationally respected and compares well with those of other countries. Figure 1-3 shows the top twenty countries ranked in order of number of reports per million inhabitants per year (average from 1st January 1998 to 30th of June 2003), based on the year when the reports were processed into the WHO database (Personal communication, WHO Uppsala 2003). The average reporting rate of the 73 countries for which data was supplied, is 76 reports per million inhabitants per year, with a range from zero to 608 reports per million inhabitants per year. Out of the 71 countries for which data was supplied the UK ranked 5th.

Figure 1-3 : The top twenty countries ranked in order of adverse drug reaction reporting rates as calculated from WHO data



Criticism of the Yellow Card scheme is also in the lay media, under-reporting rates to the scheme being discussed in *Good House Keeping*¹⁶⁸. In October 2006, *Which Magazine* ran a news story entitled “*Drugs watchdog fails public*”, which criticised the MHRA over its handling of the Northwick Park TGN 1412 incident, allegations of research misconduct made against Proctor and Gamble, and the MHRA’s alleged failure to monitor drug advertising¹⁶⁹. The MHRA was also accused to failing to take action against drugs with safety issues, such as the SSRI group of drugs¹⁷⁰ and has been recently described as “*unaccountable, slow and lacking in the necessary expertise*” by the editor of the BMJ¹⁷¹. The black triangle scheme has also been criticised, due to poor uptake of the symbol on manufacturers information¹⁷².

Others have argued that the MHRA has to balance seemingly incompatible tasks of both promoting the UK pharmaceutical industry and assuring drug safety³⁶.

1.6. Patient reporting to the Yellow Card Scheme

In 1983, following benoxaprofen's withdrawal, the CSM Working Party on Adverse Reactions considered the issue of patient reporting to the Yellow Card scheme¹⁵⁹. They concluded it was essential to obtain the expert medical opinion of the doctor treating the patient, and advised patients wishing to make a report to consult their doctor – who would make a report if appropriate. Early research conducted in the 1980s using pharmacists to distribute patient reporting forms, showed patients could report ADRs, but that the reports were lacking details¹⁷³. The authors concluded that reporting schemes should resist pressure to accept patient reporting.

In recent years patient reporting has been increasingly advocated, despite evidence for its ability to discover new safety signals being equivocal¹⁷⁴⁻¹⁷⁶. This has been driven by a number of factors. As the approach to medicines becomes more orientated to concordance, rather than an older more paternalistic view of compliance with medication, it has become politically unacceptable to exclude patients from reporting schemes. Falls in the numbers of reports from professionals, and continued complaints about under-reporting and filtering of patients' complaints by health professionals, have also led to a renewed look at patient reporting.

Studies have shown that patients, including older patients, can recognise adverse reactions which are similar to, although sometimes less serious, than those reported by professionals¹⁷⁷⁻

¹⁸¹. Patients' also appear willing to participate in such reporting scheme¹⁸².

Patient reporting of ADRs to OTC medicines, facilitated by pharmacists, has also been shown to find ADRs, and inappropriate use of OTC medicines, that may be of interest to regulatory authorities^{183,184}.

Supporters suggest that patient reporting may discover safety signals earlier than healthcare professional reporting¹⁸⁵. A study of patient reports accepted via a telephone information service in Holland compared patient reports of ADRs to paroxetine to health professional reports¹⁸⁶. Although the proportion of new unlabelled reactions reported was similar for both patient and professional reports (21% vs 18%), the mean lag time for all reactions was 229 days less for the patient reports, and 273 days less for nine new unlabelled reactions. Patient reporting detected ADRs earlier, but patient reports were often crude and incomplete compared to professional ADR reports. Hammond et al¹⁸⁷ examined the quality of patient reports and healthcare professional reports received by GlaxoSmithKline during 2003, finding that the numbers of high and moderate quality reports were similar. They suggested that consumer reports may be capable of providing reports that are useful in signal generation.

E-mails elicited after a BBC documentary examining the safety of selective serotonin reuptake inhibitors (SSRIs) were found deficient in key data, such as name, sex, and age of the informant, dosage or duration of treatment, concurrent medication and diagnosis¹⁸⁸, however a later study comparing patient reports to Yellow Card reports showed patient reports were much richer in terms of their description of the nature, severity, and significance of reactions than professionals' ADR reports¹⁸⁹. Patient reports may capture the personal experience of adverse reactions in a way that professional reports cannot, and the narrative 'richness' of such reports may be important in guiding regulatory authorities towards reactions that would otherwise be missed or dismissed as trivial. Patient reporting is also likely to be influenced by the perception of risks that patients have and the information

provided to them about the safety of medicines¹⁹⁰⁻¹⁹³. Patients' have differing views of risk than health professionals¹⁹⁴.

Little has been published about national reporting systems experience of patient reporting, however the Netherlands Pharmacovigilance centre reported that patient reports contained sufficient medical information for pharmacovigilance purposes, and reported serious reactions more than professional reports¹⁹⁵.

However, others have argued that relations between patients and their doctors could be disrupted if regulatory authorities investigated reports without the involvement of the prescribing doctor¹³⁴. As recently as 2002, a Lancet editorial wrote "*without careful thought this latest move to involve patients in health care could end up overwhelming an already struggling system, and risk being seen as politically rather than scientifically driven*"¹⁷¹.

However, the under-reporting of ADRs by health professionals continues to be a concern. When the Netherlands pharmacovigilance centre started collecting patient reports, half the patients in the first six months of the scheme said that the fact their health professional did not listen to their complaint about a possible ADR, or had a lack of confidence that a report would be submitted, was a reason for filing their report¹⁷⁶.

The MHRA's experience of patient reporting is relatively recent. Small pilots of patient reporting were launched with NHS Direct telephone service in April 2003, but received a limited number of reports. Patient groups argued that professional involvement had prevented patients' qualitative experiences from being collected. The gate keeping role professionals have held in reporting adverse drug reactions can act as a filter, removing ADRs deemed important by the general public. Regulatory authorities are left open to the accusation that genuine public concerns are not reported. In 2004, *The Independent Review of Access to the*

Yellow Card Scheme recommended that a direct patient reporting system should be introduced¹⁵⁶.

Re-launched as a pilot scheme in January 2005, and rolled out nationally in October 2005, the revised patient reporting scheme includes an electronic form for reporting adverse drug reactions, a telephone number and a paper form. Evaluation of the first six months of reports (n=407) showed that there was no difference in the number of serious reactions compared to health professionals, although patients did focus on more well established drugs, rather than new drugs or vaccines. Patient reports were less complete, but there was no difference in causality assessments¹⁹⁶. A review paper by members of the CSM Patient Reporting ADR Group of the CSM concluded that although there was a lack of evaluations of patient reporting, international experience suggested new ADRs had been discovered¹⁹⁷.

The MHRA started an evaluation of the patient reporting scheme commencing in September of 2007, which will investigate patient experience and involvement in the scheme, as well as the scientific value of the reports. It is likely that patient reporting will perform an increasingly important additional role to professional reporting,. It is not known what, if any, effect the introduction of patient reporting will have on professional ADR reporting.

1.7. Regional Yellow Card Centres

While the Yellow Card scheme is centrally administered by the MHRA at a national level, five Yellow Card Centres (YCC) exist in the United Kingdom: West Midlands, Mersey, Northern and Yorkshire, Wales, and Scotland. YCCs were established in order to stimulate ADR reporting, to improve communication, answer queries and provide information about ADR reporting to reporters at a local level, often through the publication of local drug safety bulletins. YCCs are usually based within local medicines information centres or university departments of clinical pharmacology; the local contact and expert advice provided to clinical

colleagues in regions by clinical pharmacologists and pharmacists employed by YCCs is particularly valued. Additional roles undertaken by YCCs include the provision of educational events about ADR reporting and the Yellow Card Scheme¹⁹⁸, as well as undertaking research within the area of ADRs and drug safety. All YCCs have websites reachable from the main MHRA website or <http://www.yellowcard.gov.uk>.

Regional centres were examined by the CSM in 1983¹⁵⁹. At the time three regional centres existed: the West Midlands, the Northern region, and Wales. Although, the report acknowledged a risk of regional centres becoming an additional bureaucratic tier delaying the receipt of adverse drug reactions, they welcomed the centres and felt that the enthusiasm and commitment of the centres would help keep an interest in reporting – especially via undergraduate and postgraduate teaching. Local information and feedback was considered important.

The Independent Review of Access to the Yellow Card Scheme advised that YCCs needed to be more closely integrated with the Yellow Card scheme. In the past, Yellow Cards sent to YCCs were transcribed into local databases and forwarded to the MHRA. The report argued that all Yellow Cards should be collated centrally, with copies of Yellow Cards being returned to the relevant YCC. Concerns were expressed that this would disconnect the YCCs from their reporting base, and lose the local element of the scheme. However, from April 2006, all Yellow Cards were collected centrally, with YCCs being supplied with information to follow up local reports if further information is required from a reporter. Given the review's support for the educational role of YCCs, it is expected their information provision and educational roles will expand. Existing YCCs may extend their coverage to other areas, and additional YCCs may be formed.

From 1998 to 2001 the MHRA and Trent NHS ran a pilot Paediatric Regional Monitoring Centre (PRMC) – with similar activities to the other existing regional monitoring centres in

the UK. The first twelve months appeared to show an increase in performance in the region, with the number of paediatric reports from the region doubling in the first year.¹⁹⁹ After three years of operation, the scheme attracted 456 Yellow cards, compared to a comparator region without a regional centre which attracted 155 Yellow Cards²⁰⁰.

The Mersey YCC has published data linking a series of educational events at the start of introduction of pharmacist reporting to an increased number of hospital pharmacists Yellow Card reports within their region¹⁹⁸, although this was an informal study without controls.

Regional centres for pharmacovigilance purposes are also used in other countries, such as Canada²⁰¹, France²⁰², Germany²⁰³ and Norway²⁰⁴.

1.7.1. History of the West Midlands Yellow Card Centre

The West Midlands Centre for Adverse Drug Reactions was first incarnated as The West Midlands Adverse Drug Reaction Study Group in 1973²⁰⁵. It was a multidisciplinary venture run by doctors and pharmacists. The group issued locally-addressed CSM Yellow Cards to be used by hospital doctors and ward pharmacists throughout the West Midlands region. Completed cards were evaluated to see if further information was required and the cards and any relevant information sent on to the CSM. Information about similar reports, appropriate papers and a thank you letter were issued to each reporter, in addition to the standard letter issued by the CSM on receipt of the card in London.

The study group had the aim of increasing adverse drug reaction reports to the CSM. Three mechanisms were proposed:

- Stimulate interest in adverse drug reactions in doctors and pharmacists
- Provide rapid and useful feedback to doctors reporting a reaction.
- Disseminating information through a bulletin.

The group also provided educational material to reporters in the form of bulletins supplied to doctors and pharmacists within the region, and educational meetings held in postgraduate medical centres throughout the region. Brief newsletters were also issued describing reports of particular interest.

Since 1993, the centre has been run from City Hospital, Birmingham. The centre collected Yellow Cards throughout the region until the 1st of April 2006, when Yellow Card reporting was moved to a central location. The centre is involved in educating healthcare professionals at the undergraduate and postgraduate level throughout the West Midlands. The Centre also issues a bulletin entitled *Re:action*.

1.7.2. Prescription-event Monitoring (PEM)

Another complimentary drug safety scheme exists within the UK called prescription-event monitoring (PEM) based at the Drug Safety Research Unit (DSRU) established in 1980. PEM's aim was to recruit the first 10,000 patient to received a newly marketed drug so that any adverse event that occurred in more than 1 in 10,000 patients would be reliably identified²⁰⁶.

The DSRU obtains electronic copies of all prescriptions issued for drugs being monitored from the Prescription Pricing Division of the NHS, allowing the collection of exposure data for 20,000 to 30,000 patients. This is compiled into a computerised longitudinal database of prescribers and patients, and after approximately 6 months the DSRU sends out a "Green Card" questionnaire seeking any events that had occurred in patients since the drug was first prescribed. Events include new diagnoses, referrals or admissions to hospital, unexplained deteriorations and improvements in the patient, changed laboratory values, and any other events noticeable to be recorded in the notes. Upon receipt of the forms, data is anonymized and subjected to analysis.

It is important to note although the scheme has some similarities with the Yellow Card scheme, there are important differences. GPs are requested to report any events, not just suspected ADRs, although they can indicate if they feel events are related to the drug in question. GPs are also not paid for their reports, and a limit is set of 4 Green Cards per month in order to prevent GPs overload. When follow-up is required for further information, GPs are offered a fee for completion.

In contrast to the Yellow Card scheme, which can find signals of previously unrecognised problems for any marketed drugs, PEM can only focus on a few drugs at any one time. However, while the Yellow Card scheme suffers from under-reporting and cannot measure the incidence of adverse reaction, PEM can give some measure of frequency and give a more detailed picture of reactions that might emerge. In that respect the two schemes are complementary to each other.

PEM also suffers from some under-reporting (with average participation rates of 58%), although this response rate is much higher than reporting rates to the Yellow Card scheme. The scheme also looks at prescribed medication, and does not routinely examine compliance with medication. PEM currently is not able to examine the prescribing of medicines within hospitals, although there have been attempts develop intensive monitoring schemes of new drugs within hospitals involving clinical pharmacists²⁰⁷.

1.8. Pharmacists' involvement in spontaneous reporting

Pharmacists' involvement in drug safety has not always been glorious. In 1977 a case was discussed in parliament of a pharmacist who was still supplying practolol to a patient, 12 months after it had been withdrawn from sale²⁰⁸. However, pharmacists have argued for greater involvement in the Yellow Card scheme for a number of years.

In 1985, The Pharmaceutical Society proposed a “*pink card*” scheme to run in conjunction with the Yellow Card scheme²⁰⁹. The proposed scheme would have solicited pink cards from community pharmacists for suspected ADRs reported either by patients, or ADRs noted by the pharmacist. Reports due to a prescribed medicine would have been sent to the GP, and copies of the pink cards would have been sent to the Pharmaceutical Society. Reports would have been monitored on a weekly basis and the CSM informed when a potentially serious reaction was reported, or when three reports of one particular reaction had been reported. The Pharmaceutical Society requested funding from the CSM, which was not forthcoming.

The RPSGB requested the involvement of pharmacists in the Yellow Card scheme on the basis of pharmacists’ accessibility to patients, knowledge of drugs and knowledge of any non-prescription drugs being taken.

The role of hospital pharmacists within ADR reporting started to develop in the 1970s within the UK. A clinical pharmacologist, on the Committee on Safety of Drugs, noting in 1970 the improvement in pharmacists’ training and knowledge and the role that some hospitals pharmacists were taking in monitoring of adverse reactions to drugs¹⁵.

One of the earliest examinations of the role of pharmacists in ADR reporting was that performed by the West Midlands Adverse Drug Reaction Study Group, which had been established in 1973 by interested drug information pharmacists and medical staff²¹⁰. Up to 32% of drug information enquiries in the West Midlands region related to ADRs. Between January 1978 and January 1979 the group received 237 reports²⁰⁵. Pharmacists were involved in 80% of the reports, either by filling in the report and seeking a doctor’s signature (24%), after requests for information about adverse drug reactions (33%) and after a pharmacist’s recommendation to a doctor to report during a ward rounds or clinicians rounds (23%). The three hospitals in the region with active pharmacist involvement were responsible for 40% of all reports in the region. Similar schemes were run in other areas at this time, such as the one

run by the Leicester Area Drug Information Centre, which was started in 1977 – and in which over half of the ADR reports involved a hospital pharmacist²¹¹.

The Hereford Hospital Prescribing Study suggested that routine monitoring of prescription sheets for the prescribing of antidotes or drug discontinuations by ward pharmacists could be used to identify ADRs ²¹², as did a study run at Derbyshire Royal Infirmary in 1981²¹³. However, at the start of the 1980s, despite pharmacists being able to report in other European states, the role of pharmacists appeared to be restricted to encouraging the reporting of ADRs by doctors²¹⁰. A national survey performed in 1979 sent to pharmaceutical officers in the UK showed that over 82 percent of pharmacy departments held supplies of Yellow Cards, although only 16% of ward pharmacists carried them to wards²¹⁴. Although only one percent of chief pharmaceutical officers reported that pharmacists took the initiative to complete a Yellow Card for signing by a doctor, there were greater levels of pharmacy encouragement of reporting (30%) and monitoring of patients (17%). However, 71% of respondents wanted greater involvement with the Yellow Card scheme. Training and knowledge were identified as factors that might limit pharmacists' contribution to ADR reporting,

In 1983, the CSM's Working Party on Adverse Reactions, established in the wake of the withdrawal of the anti-arthritic drug benoxaprofen, suggested that hospital pharmacists might have a role in assisting doctors to report adverse reactions to the Yellow Card scheme¹⁵⁹.

During the 1980s hospital pharmacists became more clinically involved with patient care. The industrial nature of pharmaceutical production led to a transfer of responsibility for the production of pharmaceuticals, away from pharmacists and a reduction in demand for the traditional knowledge and skill of dispensing. This led to a shift in pharmacist activity from the dispensary to the hospital ward.

A corresponding interest in ADR reporting continued throughout the 1980s²¹⁵⁻²¹⁹, especially when the role that pharmacists were playing in other countries was noted, such as in Australia²²⁰.

In 1985, the CSM Working Party on Adverse Reactions recommended that pharmacists should not be accepted as direct reporters to the Yellow Card scheme²²¹. They were supportive of the current role of pharmacists in hospital and encouraged further development of local schemes to improve ADR reporting, but held concerns about the lack pharmacists' ability to provide personal information about patients, and a description of the reaction in medical terminology. A member of the Working group felt that hospital pharmacists had a valuable role in "*cajoling*" doctors to fill in Yellow Cards, but expressed concern about pharmacists reporting reactions in his patients, without them informing him of their occurrence²²². In a chapter in Inman's *Monitoring for Drug Safety* in 1986, a Professor of Clinical Pharmacy stated²²³, "*Pharmacists lack the knowledge of clinical medicine necessary to recognise adverse drug reactions. However, their knowledge of pharmacology and toxicology should ensure a role for them in the prediction and prevention of adverse drug reactions*"

Hospital pharmacist interest in ADR reporting continued throughout the late 1980s and early 1990s²²⁴. Winstanley et al²²⁵, described in 1989, a scheme at the Royal Liverpool Hospital which led to an fivefold increase in Yellow Card reports to the MHRA. Booth et al²²⁶ in 1988 described a scheme run at the John Radcliffe hospital, Oxford, where an ADR team consisting of a pharmacist and clinical pharmacologist assessed and followed up reports of ADRs. This approach led to the detection of ADRs in 6% of patients, and some Yellow Card reporting to the MHRA, a figure that is surprising close to the incidence of later more rigorous studies of the incidence of ADRs⁷⁷. The Oxford Adverse Drug Reactions Scheme continued to operate on seven acute general medical wards at John Radcliffe hospital¹³⁵

during the 1990s. A part-time research pharmacist, who visited wards and investigated and evaluated reports, ran the scheme. Over a three-year period April 1990 to March 1993, 1,420 reports of ADRs were made. Pharmacists were responsible 50.4% (n=240) of ADRs suitable for reporting to the Yellow Card scheme (n=477).

In 1990 Lawson noted that studies were underway to examine if hospital pharmacist reports would enhance the value of reports from UK hospitals, although even then it was noted that such reports required the approval of the prescribing doctor¹⁶⁰. Local hospital reporting schemes continued to be publicised as good practice²²⁷, and national surveys showed their widespread development.

In hospital pharmacy, one of the ways in which pharmacists have been involved in adverse drug reaction monitoring is chart review. A recent systematic review of chart review as a method of detection of adverse drug reactions compared pharmacist chart review with other clinicians performing chart review.²²⁸ Although, the number of included studies was low (13), a statistically significant difference in favour of pharmacist chart review was apparent. Such studies underline the fact that pharmacists have something to add to adverse drug reaction reporting, and have the ability to make a contribution.

A prospective crossover study of pharmacists providing academic detailing compared pharmacist ADEs reported by physicians and nurses spontaneously, compared to those reported when a pharmacist participated in daily ward rounds, chart review and soliciting additional information from nurses and physicians²²⁹. The intervention led to a 10-fold increase in ADEs compared to the control.

Interest in community pharmacist reporting had continued, with a 1991 study suggesting a community pharmacist-based scheme could contribute towards reporting minor and more serious ADR reports²³⁰. Whittlesea et al²³¹, performed a 17-month study from August 1992,

in 98 participating community pharmacies. Twenty-one pharmacies submitted a total of 49 ADR reports, twelve of which were related to new drugs. Although, the scheme only elicited reports from a minority of pharmacists, it did show that community pharmacy was capable of producing reports. In any case, doctor involvement in the Yellow Card scheme has also been skewed, with many doctors never submitting a report²³², Khan and Archer found pharmacists keen to be involved in ADR reporting, and obtained 96 ADR reports in a 6 week study²³³. In 1993, a series of studies by Wolfson, Booth, and Roberts²³⁴, supported by a historical overview of the community pharmacist's role in ADR reporting²³⁵, set out a case for the introduction of community pharmacy reporting. *The Pharmaceutical Journal* editorial that week hoped that the work would tip the balance in favour of pharmacist reporting²³⁶.

Internationally, pharmacist reporting had been widely accepted outside of the UK^{201,237}, a survey from 1986 of national regulatory bodies describing pharmacist ADR reporting as standard practice²³⁸. By the late 1980s pharmacist reporting was accepted in Australia, Belgium, France, West Germany, Ireland, New Zealand, and the United States; the United Kingdom, along with Denmark, Finland, Netherlands, Sweden and the UK excluding reporters²³⁹. After the introduction of pharmacy ADR reporting in the Netherlands, pharmacists contributed 40% of all reports²⁴⁰.

In the United States hospital pharmacists have made a large contribution to ADR reporting, with a keen interest setting up ADR surveillance systems²⁴¹⁻²⁴⁷. In 1989, the American Society of Health-System Pharmacists (ASHP) produced guidelines on the monitoring and reporting of ADRs²⁴⁸, a survey in 1992 showing 90% of surveyed hospitals were complying with the guidelines²⁴⁹. In contrast, the United Kingdom Clinical Pharmacy Association 1996 Statement on Pharmaceutical Care made no explicit mention of ADRs, or the reporting of ADRs²⁵⁰.

1.8.1. Performance of pharmacists in the Yellow Card scheme

An MHRA pilot of hospital pharmacist ADR reporting in the area run by the Northern YCC during 1992-1993 investigated if they could add value to the Yellow Card scheme²⁵¹. Assessments of Yellow Card completeness and causality showed reports were equivalent in nature to those from medical staff, although there were statistically significant differences in the types of ADRs and drugs reports. Hospital pharmacists were statistically more likely to report serious ADRs and less likely to reports ADRs to black triangle drugs. An interim report of this study described how Yellow Cards from hospitals in the Northern region had been increased by 50%²⁵².

On the basis of this pilot project, the decision was made to extend the Yellow Card to hospital pharmacists²⁵³.

Results of the first year of pharmacist reporting were published in *Current Problems in Pharmacovigilance*²⁵⁴ and *The Pharmaceutical Journal*²⁵⁵. Between April 1997 and March 1998, 3.6% of the MHRA's Yellow Card reports were submitted by hospital pharmacists. Compared to hospital doctors, they reported a lower proportion of black triangle drugs (68% versus 57%; $p < 0.0136$) and higher levels of serious reactions (78% versus 64%; $p < 0.0001$). The proportion of fatal reports was comparable with that of doctors. Interestingly, the proportion of reports requiring MHRA follow-up for further information was statistically significantly lower than that of doctors (12% versus 18 %; $p < 0.0004$), however this may have been due to the nature of the reports submitted by pharmacists, rather than any greater ability to provide information. Indeed, hospital pharmacists reported serious effects to well established drugs, such as bleeds associated with diclofenac, aspirin, or warfarin, which might not trigger follow-up by the MHRA as compared to the black triangle drugs reported by medical staff. Sixty percent of all reports came from just 10 counties within the UK, six of which were within areas covered by MHRA YCCs. Hospital doctor reporting increased over

the same period, indicating that the hospital pharmacist reporting was additional. Davis et al²⁵⁵ argued that differences in ADR reporting between hospital doctors and hospital pharmacists could have been explained by pharmacists either reporting cases which were more clear-cut in terms of causality due to lack of confidence, or perhaps focusing on serious reactions that they wished draw attention to.

The regional variation in reporting was put down to variation in the numbers of enthusiastic advocates of reporting within different hospitals. This point would tally with the sizable effect that local reporting schemes can have on reporting rates within hospitals^{218,225,226,256,257}, which may have accounted for the regional variation.

Over the first five years of the Yellow Card scheme reports from hospital pharmacists increased from 713 per year to 1858 in 2001, although the MHRA expressed disappointment at this level of reporting given the population of 5,000 hospital pharmacists²⁵⁸.

Community Pharmacists were admitted to the Yellow Card scheme in 1999²⁵⁹, with the chairman of the CSM stating that he had *“every confidence that community pharmacists adverse drug reaction reporting is a worthwhile enterprise”*²⁶⁰.

At the time of the introduction of formal ADR reporting by hospital pharmacists to the Yellow Card scheme a demonstration scheme was also launched to evaluate the potential of community pharmacist ADR reporting. The evaluation was run in the four regional YCC centres available at that time, Community pharmacists were asked to report using the CSM's criteria for reporting, as well as asking them to focus on over-the-counter and herbals products.

Between April 1st 1997 and March 31 1998, 3,621 were submitted to the four YCCs, of which 96 (3%) were from community pharmacy²⁶¹.

It was found that there was no difference between the proportions of serious reactions reported by community pharmacist (40%) and GPs (40%). There was also a non-statistically significance difference between reports for black triangle drugs between community pharmacists (29%) and GPs (39%). Interestingly pharmacists did submit a statistically significant higher proportion of ADR reports related to herbals (4.2% versus 0.4%; $p < 0.001$), and for reports of generic inequivalence (3.1% versus 0.6%; $p < 0.01$). Community pharmacists' reports required follow-up requests less often. There were no differences between community pharmacist ADR reports and GP ADR reports, in terms of either causality or completeness of reports. On the basis of this evaluation the CSM were supportive of the extension of Yellow Card reporting to community pharmacists.

An assessment of community pharmacist reporting to the Yellow Card scheme was published in 2002²⁵⁸. Community pharmacists were reporting around 500 ADR reports per year, a disappointing figure considering over 20,000 community pharmacists were in practice. Of 258 herbal reports, only 13% had been received from community pharmacists.

1.9. Attitudes of healthcare professionals to ADR reporting

The effectiveness of any spontaneous reporting scheme depends on the continued supply of reports of suspected ADRs to regulatory authorities. Therefore the attitudes and behaviour of reporters to the Yellow Card schemes are a subject of academic and regulatory interest.

1.9.1. Doctors attitudes to ADR reporting

Bill Inman, the founder of the Yellow Card scheme, made one of the first theoretical forays into reasons why doctors failed to report ADRs in 1976²⁶². Noting that the reasons for non-reporting were likely to be numerous and complex, he suggested that amongst them lay the "Seven Sins" (Table 1-6).

Table 1-6 : Inman's "Seven Sins" preventing adverse drug reaction reporting

Complacency	Encouraged by one-sided drug promotion and the belief that only safe drugs are allowed on the market
Fear	Of possible involvement in litigation or investigation of prescribing costs by the Health departments
Guilt	At having administered the treatment which may have harmed a patient
Ambition	To collect and publish a personal series of cases
Ignorance	At the Committee's requirements for reporting
Diffidence	About reporting mere suspicions
Indifference	On the part of an individual doctor to his essential role as a clinical investigator who should be contributing to the general advancement of medical knowledge

Drury²⁶³ in 1977 listed five possible reasons for low recognition of ADRs by GPs in the UK:

- Lack of knowledge
- Diagnostic difficulty
- Denial
- Constraints of time and number
- Low patient reporting

Inman's "*Seven Sins*" have been used to inform surveys of medical attitudes towards spontaneous reporting.

Lumley's 1986 study of GP under-reporting also discussed some of the reasons given for the non-reporting of adverse drug reactions¹³⁶. The most frequent reason given for not reporting was that the ADR was expected or well known (58%), too trivial (11%), or the doctor was uncertain that the reaction was a true ADR (14%). The study was unable to account for reasons for why individual reactions may have not been reported.

A Northern regional monitoring centre study, designed to determine the opinions of doctors within high and low reporting districts, sent a questionnaire to 1600 hospital doctors and principal GPs in two high and two low reporting districts²⁶⁴. The study obtained a good

response rate (74%), although response rates were lower in GPs and juniors in low reporting districts. Perceptions of their reporting rates and attitudes and knowledge of the Yellow Card scheme were similar, although those in low reporting districts wrote significantly higher levels of prescriptions and a significant proportion of this group expressed concern about their identity being revealed to the CSM. There was widespread ignorance of the black triangle symbol. Interestingly, GPs were more likely to suggest a fee would improve their reporting. Despite some misunderstandings about the Yellow Card scheme, there was good awareness of the primary purpose of the scheme to identify new ADRs. Severity, newness of a drug, and unusualness were strong factors in making the decision to report. A majority felt ADR reporting was a professional obligation. Other factors reducing ADR reporting were noted to be lack of time, lack of an easier method of reporting, the potential for being “badgered” by the CSM, and serious well-known reactions.

Belton’s 1995 UK survey of 500 doctors, obtained a lower response (57%) and failed to confirm Inman’s “Seven Sins” as reasons for non-reporting²⁶⁵. Again seriousness of a reaction, unusualness of a reaction and newness of a drug were factors increasing the likelihood of an ADR report. A significant number of doctors also wanted certainty that the drug was the causative agent. Of Inman’s “Seven Sins”, only lethargy seemed to be significantly cited by doctors, 50% of whom suggested being “to busy to send a report” as a reason for non-reporting. There was mixed understanding of the Yellow Card scheme, with most understood the primary purpose. Lack of confidence in diagnosing iatrogenic illness was also highlighted, especially in hospital reporting. Unavailability of forms was also an issue for some reporters (21%).

Belton’s survey was criticised by Inman²⁶⁶, who felt the final number of respondents to the survey was low, and that those who suffered from some of his “Seven Sins” were unlikely to

respond to a survey of this nature. Inman strongly argued that case series collection by young doctors was behind under-reporting in hospitals.

McGettigan et al²⁶⁷ examined Inman's hypothesis concerning junior doctors collecting case reports, but a year long review of medical journals did not find a single case report published by a population of junior medical staff in a scheme to improve ADR reporting, suggesting this was not an important deterrent. Deterrents discovered, listed by more than 20% or more of doctors, were the unavailability of cards, lack of time, and lack of knowledge about how to report. A clear preference for reporting unusual ADRs, and ADRs to new drugs was also seen.

Later examinations have been performed outside of the UK. Belton et al²⁶⁸ conducted a survey of 1% of EU medical staff, with a response rates ranging from 19.7% to 77% dependent on the country. Large number of doctors noted they had never reported an ADR to either regulatory authorities or companies. Seriousness and unusualness of the ADR were considered important factors in deciding when to report. Confidence in the diagnosis was also required by many. Ignorance of reporting schemes methods of reporting or lack of reporting cards was common in many countries. Reporting criteria varied across states, but the majority agreed that serious reactions and all reactions to new drugs should be reported. The survey did appear to discount some possible inhibitors of reporting such as: reluctance to disclose confidential material, fear of legal liability, embarrassment at admitting harm, or the collection of a case series.

A survey of Dutch physicians²⁶⁹ (1442, 73% response rate) listed the top three reasons for not reporting as: uncertainty if the reaction was caused by a drug (72%), the ADR being trivial (75%) or too well-known (93%). One in five were unaware of the need to report reactions. Or how to do so. Thirty-eight percent felt they did not have the time to report, and

only 26% knew which ADRs to report. Serious ADRs, unusual ADRs and ADRs to new drugs were associated with an increase chance of reporting.

An Italian study²⁷⁰ looked at the attitudes of doctors in a very low reporting region of Italy. Letter sent to all GPs and 58 hospital consultants, with a 59% return rate. The majority had seen ADRs (77%), but half of the respondents indicated they did not report ADRs. Those that did report listed pharmaceutical companies (43.5%), the official route via the Area Health Authority (10%) and scientific journals (2.9%) as their reporting route. Important factors linked to reporting included the unusualness of the ADR, the involvement of a new drug, as well as doctor awareness of new ADRs.. Reporting was a legal requirement in Italy at this time, and was cited by 20.4% of respondents. Negative factors mitigating against reporting was the clinical negligibility of the reactions (79.2%), an awareness of similar reactions (28%), unavailability of the ADR reporting form (16%) and uncertainty about what to report (14.4%). No doctors felt reporting was useless. Unusually, time was only cited by 4.8% of respondents as an issue. With regard to what to report, any reaction to any marketed drug was cited by 58.4% of respondents, however less than 60% of doctors were aware of responsibility under legislation to report all ADRs. Doctors lacked well-defined criteria to report. A smaller Italian study of GPs described uncertainty of causality (51%) and lack of time (18%) as important inhibitors of reporting²⁷¹.

Robins et al²⁷² conducted a telephone questionnaire of 104 doctors in Cape Town, South Africa. Notably, 47% of doctors did not consider a well-established and common side effect to be an ADR. GPs felt new drug reporting was important, although more than half of the respondents had never reported to the local scheme. When asked to suggest reasons for under-reporting, 58% suggested that few ADRs are seen, and when they are observed they were minor, well-established and not worth reporting. Apathy was reported by 40%, and 27% felt that doctors are too busy to find time to complete a form. Over 80% of respondents also

felt that doctors were reluctant to commit themselves when the evidence for an ADR is insufficient.

An examination of a French regional monitoring centre²⁷³ showed a statistical difference in the amount of severe reactions reported by hospital doctors compared to GPs. The higher reporting rate of hospital physicians was suggested to be an effect of training by the regional centre. GPs were suggested to be more likely to report to industry. GPs more also likely to report reactions that could be clinically diagnosed, rather than those laboratory diagnosed.

A survey by doctors.net.uk of 1220 hospital and general practitioners, commissioned by the National Audit Office, gave a number of common reasons for not reporting adverse effects of medicines. Concern about workload, reporting criteria and practical aspects of reporting were raised¹⁶⁶.

ADR reporters keen on feedback information and continuing education is of key importance. During the 1970s the CSM doubled reports when *Current Problems in Pharmacovigilance* was started¹⁵⁸.

Three case-control studies examining reporting and non-reporting doctors' attitudes towards ADR reporting have been undertaken in Spain and Portugal²⁷⁴⁻²⁷⁶. These studies demonstrated that some of Inman's "*Seven Sins*" did seem to hold, with the following beliefs reducing the odds of reporting a reaction^{275,276}:

- The belief that really serious ADRs are well documented by the time a drug is marketed.
- The belief it is impossible to determine if a drug is responsible for an ADR
- Only reporting an ADR if sure that it is related to the use of a drug.
- Belief that a single case report cannot contribute to medical knowledge.

Interestingly, it was found that male doctors were twice as likely to report ADRs as female doctors, a finding that has not been found elsewhere²⁷⁷. ADR reporting also decreased with

increasing patient load on doctors, which is consistent with Roger et al's US study²⁷⁷. Physicians' knowledge was strongly linked to the odds of a ADR report being made²⁷⁵. In a Spanish case control study it was found that 50% of doctors felt that ADRs were well-documented before marketing of a drug, the belief that all drugs being safe reducing the chances of reporting²⁷⁴. In the UK this view has been found to be held by 5% of doctors²⁶⁵. None of the studies found support for use of a financial incentive.

A US study of physician attitudes towards the FDA ADR reporting scheme found similar attitudes²⁷⁷, with a lack of knowledge about reporting, a widespread view that drugs were safe before marketing, and a view that ADR were difficult to ascribe to drug treatment. Time to report and ease of reporting were also seen as important to reporters. However, it was noticeable that legal concerns were more apparent in the US, possible due to the more litigious nature of US medicine. Non-reporters were much less likely to view ADR reporting as a professional duty than reporting doctors.

Nita et al²⁷⁸, in an Australian survey, found that serious or usual reactions were more likely to be reported, as were reactions to new drugs. Lack of time, an uncertain association, and well-documented trivial ADRs were barriers to reporting.

A German study²⁷⁹ and a Swedish study²⁸⁰ both confirmed similar findings that well-known reactions, serious reactions, and reactions to new drugs were most likely to be reported. There was also a lack of knowledge about reporting schemes, and both studies demonstrated a hesitancy to report reactions when doctor were uncertain about causation.

In summary, the attitudes of doctors to ADR reporting are an important factor in the decision to report an adverse reaction. Firstly, knowledge of the reporting scheme and the process to submit a report is necessary. However, in order to report doctors do require an awareness of the ability of drugs to cause ADRs, and once an ADR is suspected, the confidence to report a

reaction even though they may have doubts about causation. In addition, characteristics of the ADR itself can increase the likelihood of a report, such as seriousness, unusualness, and an association with a new drug. These characteristics may not always reflect the types of ADRs that regulatory agencies would like, and do lead to bias within spontaneous reporting systems.

There is also evidence that lack of knowledge of the value of an individual report can lead to reporters not valuing their reports. Some of Inman's "*Seven Sins*" do appear to hold in varying degrees, among differing reporter groups, but time, workload, and the perceived difficulty of the reporting pressures appear to inhibit reporting – although reporters see these factors as less important. Legal concerns about reporting appear to have a low influence on the decision to report, especially in the UK. While the use of a fee to stimulate reporting appears is relatively unstudied, the majority of doctors do view ADR reporting as a professional activity. Education about pharmacovigilance is almost universally seen as a way of changing the attitudes of doctors.

1.9.2. Reporter characteristics

Another area of interest to researchers investigating the reporting of ADRs by doctors has involved investigating the characteristics of reporters or groups of reporters.

Speirs et al²³² in their report on the demography of the UK register of spontaneous reports noted that of 122,000 registered doctors in the UK in registered at some point within the period 1972-1980, only 19,749 (16%) doctors had used the yellow card scheme. Most reports are sent in by doctors who have sent in more than one report. Analysis of a smaller sample of reporting doctors appeared to show that those qualified for 0 to 5 years and those qualified for more than 40 years were reporting statistically fewer Yellow Cards than would be expected, although it was not know if this was due to differences in patient contact.

Bateman et al²⁸¹ examined geographical differences in ADR reporting in the Northern Region of the UK. After standardising for clinical activity, it was found that there was a large variation in hospital reporting rates and reporting rates of GPs from various health districts in the region. They found no correlation between reporting rates of GPs and reporting rates of hospital doctors within the same locality. They were unable to account for the variations in reporting rates.

Inman and Pearce²⁸² examined the performance of doctors in supplying information to the DSRU PEM scheme (*op cite*), based on their prescribing activity. Prescribers were divided into six groups, based on their prescribing of a number of drugs used in 21 PEM studies undertaken between September 1984 and June 1991. 543,788 Green Cards were sent to 28,402 GPs, with an average response rate of 53%. There was a large variation in the level of prescribing of drugs between GPs, with 10% of doctors being responsible for the prescribing of 42% of the drugs. One percent of very high prescribers were responsible for 10% of all prescribing of the study's drugs.

The response rate for Green Card varied between the different groups of GPs. The heaviest prescribers had a response rate of 44%, and 1% of very high prescribers had a response rate of 34%. Inman's analysis appeared to suggest that those most likely to prescribe new drugs, and more susceptible to the pharmaceutical industry's promotional techniques, were the least likely to engage with post-marketing surveillance.

More recently Clark et al²⁸³ examined prescribing rates in the 15 administrative regions of the NHS in Scotland. Their primary analysis consisted of 14 medications that appeared in the top ten reported drugs for the years 2000 and 2001. Vaccines were not included in the analysis, since their supply was centrally controlled. Short-term hospital only drugs, unlikely to have originated from primary care prescribing, were also excluded. An estimated exposure of the population to these drugs was expressed in reports per 1000 prescriptions, and for each area a

reporting rate for those drugs was calculated expressed as the number of Yellow Card reports per million population. Importantly, the study used primary care prescribing data, and yet used Yellow Card reports sourced from both primary care and hospitals.

They found that there was a significant positive correlation between the number of ADR reports per million population and the number of prescriptions per thousand population ($r = 0.66$, $p = 0.04$), implying that 44% of the observed variations in reporting rates could be attributed to variations in the prescribing rates of the drugs. After excluding the largest health board, which comprised 44% of the total population and was suspected to have a disproportion effect on correlation coefficients, the correlation increased slightly and remained significant ($r = 0.74$, $p = 0.02$). In contrast to Inman's work this suggested that higher levels of prescribing were related to higher levels of reporting adverse drug reactions. Alvarez-Requejo et al¹⁴² indirectly attempted to find if workload effected ADR reporting by comparing GP patient load against reporting rates, but found a positive correlation (OR 1.03) – although they felt this could be due to the fact that the GPs in their scheme were all rural, without heavy case loads.

1.9.3. Interventions to increase doctors' ADR reporting

The Rhode Island Adverse Drug Reporting Project was established in 1986 in order to respond to concern about the under-reporting of ADRs to the FDA's reporting system. The scheme was designed to act as an intermediate stage between the FDA and the reporters in the state, in a similar way to the Yellow Card centres in the United Kingdom. After designing and distributing a simplified ADR reporting card meeting minimum FDA reporting requirements, the department promoted the scheme vigorously via professional education, direct mailings, presentations, advertisements, and articles in local medical periodicals. The project also had a telephone support line for reporters, and reporters received personalised and localised feedback, along with aggregate information on reports received by the project.

Analysis of the changes in reporting rates, compared to the rest of the US, showed that the local reporting project had had a major effect on reporting. After the start of the project the number of ADR reported per million population in Rhode Island increased, while reports from the rest of the US remained flat ($p < 0.001$). Comparing reports made directly to the FDA, Rhode Island produced a 17-fold increase in the numbers of reports submitted. From 1981 to 1985, direct reports average 11.6 per year. By 1988, there were 201 direct reports made in the state of Rhode Island, reversing the former situation of direct reports to the FDA forming a minority of all reports. Before the study Rhode Island accounted for 0.4% of the US population, and accounted for 0.4% of the ADR reports received by the FDA between 1981 to 1985. In 1988, it accounted for 3.5% of all direct reports to the FDA. Statistically significant increases in the number of serious ADR reports were also seen. A pre-scheme survey and post-scheme survey of physicians in Rhode Island showed an increase in familiarity of the FDA reporting scheme from 55% to 85% ($p < 0.001$) and an increase in familiarity with the reporting forms and reporting guidelines from 39% to 69% ($p < 0.001$). It appears that on cessation of the scheme, reporting fell back to its previous level²⁸⁴.

Figueiras et al²⁸⁵ evaluated the effectiveness of educational outreach visits for improving ADR reporting physicians in Northern Portugal. The educational intervention was based on their previous research into attitudes to ADR reporting, and used Inman's "*Seven Sins*"²⁶² as a model. The intervention was based on outreach visits, reminder cards and report forms, with outreach visits consisting of 1 hour 2 part presentation made to physicians during their weekly meetings, where groups of between 10 to 20 individuals were present. Randomisation was not based on physicians, but on spatial clustering around geographically areas served by hospitals and associated outpatient centres. The intervention led to a 10-fold increase in reporting rates (95% CI, 3.81-27.51), the effect of which was highest in the first 4 months after the intervention. An attenuated effect lasted for a year, and at 13 to 16 months

post intervention no difference existed between the control physicians and the intervention group. It is not known if further educational events would have boosted reporting again. This study was well conducted, avoiding the risks of cross contamination between the control and intervention group, and does give some re-assurance that effects seen in studies without control groups are a result of interventions.

McGettigan et al²⁶⁷ intervened in a large teaching hospital in Dublin, by placing Yellow Cards at the end of patients' beds upon their admission. Cards were also sent to each prescriber and made available in wards, doctor's offices, and clinics within the hospital. Prescribers were reminded by direct contact and circulars about the scheme. For the two years prior to the intervention 4 to 6 ADR reports were submitted by hospital staff per quarter. In the quarter after this intervention, 24 ADR reports were submitted. The proportion of serious reports was similar (40%), but none involved new drugs. Cessation of verbal and written reminders led to a fall in the next quarter of 14 ADR reports. Six months after cessation of placing yellow card in patients' notes, the reporting level had dropped to pre-intervention levels. Although staff turn-over may have led to the decline in reporting, without sustained verbal and written reminders ADR reporting tends to fall, even with an increased availability of Yellow Cards. McGettigan et al argued that reporting a certain number of ADRs should become a mandatory part of training for junior medical staff, and stressed the importance of developing a reporting culture.

Griffin examined the number of items of information related to drug safety (including repeated warnings and follow-up comments) produced by the CSM between 1964 and 1983, and compared that to the number of ADR reports received by the CSM over the same period²⁸⁶. Griffin argued that there was a marked correlation between the introduction of the CSM's *Current Problems* series in 1975 and an increase in the level of reporting. Griffin hypothesised that further increasing the value of feedback to reporters might produce a

further increase in reporting rates. However, Griffin's correlation does not prove causation, and other confounding factors may have led to increases in reporting during the mid-to-late 1970s, in particular the additional publicity given to ADR reporting by the practolol disaster.

The author of this thesis was also involved in a study to examine whether the provision of improved feedback of information about ADRs could lead to increased reporting. The West Midlands YCC, identified the five most common serious adverse reactions reported to their centre²⁸⁷ and produced concise fact sheets on each describing the reaction, the risk factors and the strategies for avoidance. During 2002, the centre received reports from 312 individual GPs out of 3157 in the West Midlands region. One hundred and ninety-eight of the non-reporting GPs (Group A) were randomly selected to receive a fact sheet each month, for five months from December 2003. In another arm of the study a random sample of reporting GPs (Group B) who reported one of the relevant serious ADRs were sent the matching fact sheet. During the first 6 months of the study 9 reports were received from 8 GPs (4%) from Group A, in comparison to one report from a random comparison sample of 198 non-reporting GPs (0.5%) who did not receive the sheets. ($p=0.022$, Fisher's exact test). Of the 34 reporters in group B, 6 (18%) reporting a further reaction subsequent to receiving a fact sheet. Of the 77 other reporters reporting a "*fact sheet reaction*" who were not given a card, only ten (13%) reported a subsequent reaction – although these figures were too small to test for statistical significance.

The Catalan Centre of Pharmacovigilance examined its performance from January 1983 to October 1995, in particular focusing on the effects of introducing a free quarterly ADR bulletin in 1985 and introducing a Yellow Card into physician's prescription pads within their area from 1991. Using statistical modelling for predicting future performance of the reporting scheme based on pre-intervention data, and contemporary data, they attributed a monthly mean increase in reports of 11.7 after the introduction of their ADR bulletin. The

introduction of yellow cards raised the monthly rate from 34.4 cards per month to 53.9 cards per month. Although their study did not have a control group, and their model for expected reporting rates is less reliable than a control group, their study did suggest that production of a local bulletin increased reporting rates, as did the increased availability of the Yellow Card in prescription pads. Adding Yellow Cards to prescription pads was seen as the more efficient method of creating additional reports, in comparison to the higher intellectual input of producing a bulletin. However, in the United Kingdom the majority of prescriptions are generated using a computer, which means this method of supplying Yellow Cards is less useful. The effect of introducing Yellow Cards into the prescription pad is similar to the experience in the United Kingdom¹⁰⁷.

Bracchi et al²⁸⁸ investigated the effect of a distance learning package linked to educational credits on GP and pharmacist reporting within Wales. They invited 1745 GPs and 2039 pharmacists to complete 20 multiple-choice-questions (MCQs) based on the content of a Bulletin they provided on the subject of "*Iatrogenic disease: who is responsible?*". Those who satisfactorily completed the MCQs were given two Postgraduate Educational Allowance (PGEA) credits or Continuing Postgraduate Professional Education (CPPE) hours, along with some feedback. Those who then went on to submit three yellow cards to the CSM over the next 12 months, were then able to receive a further 3 credits. Although only a minority of GPs (27%) and Pharmacists (13%) participated in the MCQs, 77% of these professionals had not participated in the Yellow Card scheme in the previous year – showing the initiative had provoked new interest in the scheme. Sixty-two percent of the GPs and 17% of the pharmacists submitted Yellow Cards in the 12 month period. During the study year, the Wales region outperformed a comparator control region (Northern) in both pharmacist ($\chi^2=15.7$, $p < 0.001$) and GP reporting ($\chi^2=37$, $p < 0.001$). Both sets of reports had higher levels of appropriate reporting than were apparent before the study was run. The authors

argued that the educational bulletin linked to educational credits influenced both the rate and appropriateness of spontaneous reporting, and suggested that such programmes should be built into continuing medical education programmes and repeated regularly if the effects was to be sustained.

The use of a fee to induce reporting of ADR reports has been periodically brought up a mechanism for increasing the number of ADR reports. Feely et al offered a small fee (three Irish pounds) to junior doctors for each Yellow Card given to a designated registrar. During the six week survey of 136 hospital beds, 150 reports were received (incidence of 9.7%) including 2 deaths and 27 life-threatening or serious ADRs. Of the 40 doctors involved, 32 indicated that the fee had been an incentive to report. In the six weeks after withdrawal of the fee 30 ADR reports were received. Although this study did show a significant increase in the level of reporting, some of the increase in reporting may well have been due to the junior doctors being aware that a study was being undertaken and the interest being paid to the study by more senior staff. In addition, it is far from clear that a similar effect would be seen if such a relatively low payment was moved into a different environment, such as a busy surgery manned by a relatively well-paid GP.

An editorial in *Prescriber*²⁸⁹, recently argued that ADR reporting should either be made a mandatory activity, or be incentivised, noting that GPs were now paid for a variety of administrative tasks. It was suggested that the Quality and Outcomes Framework provided a system within which some measure of ADR reporting could be incorporated.

1.9.4. Attitudes of pharmacists towards ADR reporting

Although hospital pharmacists have long expressed an interest in becoming official reporters to the Yellow Card scheme, the majority of hospitals pharmacists have not engaged with the Yellow Card scheme²⁵⁸.

Studies only began to focus on the attitudes of hospital pharmacists after the introduction of formal reporting to the Yellow Card scheme, studies prior to this being focused on the extent of local reporting schemes. Green et al²⁹⁰ performed a qualitative study of hospital pharmacists in the Mersey region. Although no date was given for the interviews, the paper indicated that they had taken place in the wake of the introduction of pharmacist Yellow Card reporting. Sampling attempted to a variety of clinical pharmacists throughout the region, but did allow chief pharmacists to nominate three pharmacists from within their pharmacy services – which may have introduced bias. Tape-recorded interviews were conducted by a single researcher, using a pre-piloted semi-structured questionnaire, with previous experience of qualitative interviewing techniques. A structured coded and theme development method was employed. The final sample consisted of 38 pharmacists, from a wide range of grades and varying experience. The majority had participated in the Yellow Card scheme.

Involvement in the Yellow Card scheme for some had been due to an initial novelty factor. Some were stimulated to ADRs that they strongly felt should be reported to regulatory authorities, and which otherwise not be, this finding is in support of evidence from the MHRA that hospital pharmacists tend to report more serious reactions to established drugs²⁵⁵. The circumstances a pharmacists might be found in, such as pressure of work, was also cited as affecting the decision to report. Interestingly, pharmacists did not view the MHRA in a positive light, criticising its lack of “consumer orientation” compared to the pharmaceutical industry. Some interviewees argued the MHRA had only moved towards pharmacist reporting due to a fall in the number of Yellow Cards, rather than a positive decision to recognise the role of pharmacists in drug safety, and there was a general dissatisfaction with the lack of publicity about the introduction of the scheme. The RPSGB came under particular criticism for not arguing for the introduction of pharmacists reporting earlier, although evidence exists that the RPSGB have advocated pharmacist reporting for at least 20 years²⁰⁹.

Interviewees also believed that feedback from the MHRA, in terms of outcomes from ADR reporting and the ADR reporting performance of hospitals was important. Views of the pharmaceutical industry's involvement in ADR queries was viewed favourable by interviewees, although follow-up requests for information from the industry was seen as antagonistic.

Opinions on the local YCC depended on pharmacists' proximity to the centre and their involvement with the unit. Those using them were generally supportive of the YCC, those who had not were either unaware of the centre or suggested it could play an increased role in education pharmacists about ADR reporting.

Although pharmacists were generally knowledgeable about the black triangle scheme, there was some confusion about reporting criteria. Some interviewees used their own criteria for reporting, others expressed concerns about reporting inappropriate ADRs and suggested they would seek advice from other members of the pharmacy department before completing a Yellow Card. Whether a reaction was listed in the BNF was a factor in deciding on whether a report should be made.

Although pharmacists were generally happy with the Yellow Card, Green did come across some instances of pharmacists who did not approve of the MHRA's decision to supply separate pharmacist Yellow Cards. This was seen as a lack of full support in pharmacists' reporting to the Yellow Card scheme, making them "second class" reporters. Separate pharmacist Yellow Cards have now been discontinued.

Although pharmacists felt that they worked in "teams" with medical staff and therefore would discuss reactions after discussion with medical staff, there were concerns raised about situations where there was disagreement about whether an ADR had occurred or not. Pharmacists were also concerned about the causality of the ADRs they reported, with

concerns about reporting reactions that might be unlikely or implausible. This is a finding that is in line with what we know about pharmacists reporting the Yellow Card scheme – where pharmacists tend to report more reactions to serious reactions and less reactions to black triangle drugs^{251,255}. Pharmacists also described how they looked for ADRs, sometimes by serendipitous means during ward rounds, or through medical or patient contact, at other times through strategies such as looking at why drugs have been stopped, or why other drugs had been started.

Although motivation for reporting to the scheme was present, it varied in its strength, with some recognising a lack of motivation despite awareness of the importance of the scheme.

Most interviewees stated that feedback by supply of a letter or quantification of previous reports would be sufficient, but there was some desire for feedback that would give confidence that their report had been of value, with some worried that feedback on inappropriate reports might dissuade them for reporting in the future. Interviewers who had used MHRA in their work felt a duty to contribute to the Yellow Card scheme. The MHRA's *Current Problems in Pharmacovigilance* was widely respected and read by interviewees.

Reasons for under-reporting varied from a view that reporting well known reactions might be a waste of time, that time pressures on pharmacists were preventing them from detecting ADRs (rather than the completion of a Yellow Card), and a failure to accept the Yellow Card scheme as part of everyday professional practice.

Concern was also expressed about their clinical knowledge, though not their ability to find out drug details, and training was identified as a specific area that could be addressed to improve pharmacist reporting. Those who had attended additional study days run by the local YCC appeared to have a greater understanding of the Yellow Card scheme, and corresponding increased motivation to report. Local schemes to report ADRs, departmental

meeting on ADRs, and increased time on wards were identified as possible ways to encourage reporting. Local schemes were seen as a mechanism for “*sifting*” out inappropriate ADR reports as a form of quality control.

The majority of interviewers opposed the introduction of a fee for ADR reporting, although a few welcomed the idea. Opposition to the introduction of a fee centred on the view that ADR reporting should be a professional responsibility and concern that a fee might increase inappropriate reporting.

Green drew parallels between early pharmacist involvement in the Yellow Card scheme, that of doctors, which took several years to establish. His study appeared to show that hospital pharmacists were in a transitional stage of adopting the Yellow Card scheme into professional practice, in the face of some dissuading factors – some of which could be ameliorated by training. Increased experience of the use of the Yellow Card scheme could also be self-re-enforcing if reporter feedback is designed to emphasise the utility of the Yellow Card scheme and to duly acknowledge the decision to report an ADR.

Although Green’s study was confined to one region, with a YCC, and interviewed only 38 out of a possible 200 hospital pharmacists with that region, the purpose of the study was not to produce representative data. Despite some concerns about the sampling method being led by chief pharmacists, rather than researcher priorities, the study did interview a wide variety of hospital pharmacists in terms of both grade and experience. His findings also appear to be supported by later analysis of hospital pharmacist reporting^{255,258}.

Green followed up this qualitative work in March of 1999, with a quantitative survey of 600 randomly selected hospital pharmacists from the RPSGB’s register²⁹¹. The survey was based on similar surveys performed in the medical literature^{264,265,268} and his own qualitative work²⁹⁰. The response rate, after removal of retired or non-practising pharmacists, was 51.1%

(n=305). After accounting for the mismatch between the RPSGB's hospital pharmacy register (7000) and the reported number of full time equivalent pharmacists, (4500) Green calculated his survey represented the views of 5% of hospitals pharmacists. However, given the response rate there is a possibility that the survey attracted hospital pharmacists with an interest in the subject area, potentially leading to a perhaps more enthusiastic view of the Yellow Card scheme.

Green's findings do provide an explanation for the higher proportion of serious reactions and the lower proportion of reactions to newly marketed drugs found in the MHRA's figures on pharmacists reporting²⁵⁵. Pharmacists were less clear about purpose and the nature of the Yellow Card scheme, which Green suggested explained the relative reluctance to report minor reactions to new drugs.

There was a good awareness of the Yellow Card scheme (97%), with just over half feeling they had been adequately informed about the launch. One in four respondents had submitted a Yellow Card to the scheme, an arguably higher percentage than the wider hospital pharmacist population at that time. Over a third had not reported an ADR because they knew a doctor would report it, and 1 in 5 had completed a Yellow Card for a doctor to sign.

Knowledge about the Yellow Card reporting criteria was high with 97.7% of respondents being aware that all suspected ADRs to newly marketed agents should be report, and 91.4% aware that serious reactions should be reported for established products. A majority of pharmacists (94%) noted that the scheme did not only want to receive "only proven" reactions. Although a majority of pharmacists mistakenly understood that the incidence of ADRs could be calculated by the Yellow Card scheme, they were aware of the benefits of the scheme in of identifying unrecognised ADR (98%), identifying predisposing factors (75.%), obtaining characteristics of ADRs (62.5%), and comparing the adverse effects within a therapeutic class (65.1%). Eighty-six percent of respondents felt ADR reporting was a

professional obligation, but over half (56%) felt it was clear what should be reported to the Yellow Card scheme. In comparison to doctors views, pharmacists did not find the Yellow Card scheme complicated. Interestingly, half of respondents felt ADR reporting should be a compulsory activity.

Factors that encouraged pharmacists to report ADRs included those of a serious nature (99.3%), those that were usual (98.6%), reactions to new products (99.3), and the certainty that a reaction if a true reaction (82.4%). Well-recognised reactions related to particular drugs did not encourage reporting (12.7%).

Factors that discouraged pharmacists from reporting ADRs included apprehension about sending in an inappropriate report (33.7%), lack of time to fill in a report (45.2%), lack of time to actively look for ADRs while in clinical practice (56.8%), their level of clinical knowledge making it difficult to decide whether or not an ADR has occurred (32.3%) and not feeling the need to report well recognised reactions (40.9%). Compared to Bateman et al²⁶⁴ and Belton et al's²⁶⁸ surveys of doctors, hospital pharmacists were more discouraged by a lack of time, but expressed less concern that reporting would generate additional work. Only small minorities were discouraged by issues related to the professional liaisons with doctors, such as the doctor receiving a copy of the Yellow Card (9.0%), and a lack of confidence in discussing the ADR with the prescriber (16.2%). Lack of pharmacist Yellow Cards did not appear to be a major concern (9.7%).

When given a series of example ADRs to assess, hospital pharmacists were significantly more likely to report serious reactions to new drugs or unrecognised reactions ($p < 0.0001$).

Training had been received by just over a third of respondents, mostly in the form of departmental meetings. Those who had received training were more likely to have reported an ADR, were more knowledgeable about the reporting criteria, more likely to report in line

with the criteria, and knew more about the Yellow Card scheme. Education was the only positive predictor influencing pharmacists ADR reporting, when analysed by stepwise logistic regression ($p = 0.001$). Education was also the most frequently offered solution to improving ADR reporting.

Both Green's qualitative²⁹⁰ work and quantitative work²⁹¹ showed that pharmacists are more likely to report if there was a degree of certainty about the reaction being associated with the drug. Clinical confidence in a diagnosis of a drug was a key issue for many pharmacists.

Green postulated the relatively high importance of lack of time as a discouragement to reporting, as compared to doctors, reflected different working practices between the professions, and recruitment difficulties within the pharmacy profession. Green focused on the need for education about the Yellow Card scheme, in order to develop a reporting culture which would make Yellow Card reporting an integral part of a clinical pharmacists activities. A survey of hospital pharmacist drug information departments identified lack of time and poor pharmacist attitudes to reporting as barriers to reporting, although the authors discounted this finding due to unreliability of the question in their survey²⁵⁷.

In July 1998 Swies and Wong²⁹² surveyed hospital pharmacists using a survey similarly based on the work of Belton et al²⁶⁵, and Inman's "*Seven sins*"²⁶². Using the RPSGB's professional register 548 questionnaires were sent out, with a response rate of 51%, after the removal of 66 questionnaires who did not fit the inclusion criteria or being an active hospital pharmacist. As well as asking for respondents Yellow Card activity, pharmacists were asked for information such as the hours per week spent in various activities. The majority of respondents were female, and the sample was slanted towards more senior staff, with only 17 basic grade clinical pharmacists in the study analysis. A similar percentage of pharmacists reported they had reported an ADR (28%) to that found by Green²⁹¹, although an additional

18% of hospital pharmacists claimed to have identified a reportable ADR which they had not reported.

This survey had a number of questions which were similar to Green's paper²⁹¹, pharmacists' agreed they were more likely to report a serious reaction than a trivial one (87.4%), where more likely to report a rare ADR than a common one (78.1%), and were more likely to report a black triangle drug than an established drug (84.2).

Pharmacists also reported that the more confident they were of recognising an ADR, the more likely they would have reported it (88.8%). Increased workload was cited as something that would make ADR reporting less likely (51.1%). The support of medical and pharmacy staff to report was seen as an encouraging factor (86.3%). Only a small percentage (3.5%) of pharmacists were concerned about legal liability issues arising out of Yellow Card reporting. Education and training was a common suggestion to improve reporting.

There was no statistically significant effect of gender, age, and type of hospital on self-reported involvement in the Yellow Card scheme. There was a non-statistically significant difference in reporting between those who had received training in ADR reporting. Increasing seniority was linked to an increased tendency to report ADRs ($p = 0.0008$), perhaps reflecting increasing professional confidence. Those who spent more time on the wards (21 to 30 hours) also reported the most ADRs, although again this was not statistically significant.

Swies and Wong suggested, as did Green, that pharmacists still viewed ADR reporting as an additional duty, in comparison to doctors who may view it as part of the normal duty of a doctor.

Whittlesea investigated community pharmacists' knowledge of ADR reporting via use of two part survey in 1994²⁹³. Part A of the survey looked at views of community pharmacists

towards the Yellow Card scheme, and respondents could request Part B if they wished to participate. Piloting of survey had discovered that pharmacists were reluctant to complete Part B – which was a series of ADRs which respondents were asked to decide if they were reportable. Part A was sent to a small sample of pharmacists (n=214) obtained from the RPSGB register. Part A had a response rate of 54% (n=116). The vast majority were aware of the Yellow Card scheme (98%), although 12% of respondents already thought pharmacists were able to use Yellow Cards. Only 3% of respondents were unaware of the Yellow Cards in the BNF. There was good awareness of the black triangle (83%), although only 27% of community pharmacists were aware of the MHRA's reporting criteria for black triangle drugs and severe ADRs to established drugs. A number of community pharmacists expressed a desire for additional training if they were to report suspected ADRs. Only 41 pharmacists requested Part B, and only 20 of these returned it. Assessment of the pharmacists responses showed widespread failures to recognise suspected ADRs, and differing views on the reporting of the ADRs if detected.

A 17 month study by Whittlesea²³¹ to assess the impact of a reporting scheme for community pharmacists did evaluate the opinions of pharmacists within the scheme. The majority of those taking part did not feel involvement in the scheme had harmed their relationship with GPs, with one considering it had improved the relationship.

A qualitative structured survey of 30 community pharmacists found that respondents were supportive of ADR reporting as a professional role of pharmacists²⁹⁴. However, few were aware of the reporting criteria for black triangle reporting, and few recognised the need to report unusual ADRs to established drug or ADRs associated with the use of herbal remedies. The majority of interviewees would not report ADRs caused by OTC preparations they had sold. Lack of knowledge of patients, lack of a fee, and lack of time were cited by some

respondents as inhibitors. One respondent erroneously believed doctors were paid for reporting ADRs.

Houghton et al, surveyed the attitudes of pharmacists and GPs towards ADR reporting during the CSM's demonstration scheme of community pharmacy reporting²⁹⁵. The survey found 90% of GPs were supportive of pharmacist ADR reporting. Reasons for not reporting ADRs found during the study included the ADR was a recognised reaction (64%), uncertainty the ADR was caused by the drug (24%) and, the reaction had already been reported by the GP (20%). Ninety-four percent of community pharmacists stated it was the pharmacists' responsibility to report ADRs.

A survey of 793 US pharmacists²⁹⁶ with a 40% response rate, found 82 percent of pharmacists had been aware of an ADR in the previous year (41% of which were serious in nature aware of a serious reaction. Hospital pharmacists more likely to be aware of serious reactions, while community pharmacists had higher rates of suspected ADRs due to OTC products and therapeutic inequivalence. Hospital pharmacists found information about ADRs from physicians, while community pharmacists found ADRs from patients. Younger pharmacists were more likely to contact physicians about ADRs. There was a high level of awareness of the FDA reporting scheme (77%), but hospital pharmacists were statistically significantly more aware. Younger graduates less familiar with the scheme; 25% of recent graduates did not know how to report. Community pharmacists were less likely to report than hospital pharmacists, and less likely to have forms available.

An exploration of pharmacists views in Norway was undertaken both prior and post the implementation of pharmacist reporting to the Norwegian national ADR reporting scheme²⁰⁴. An active group was recruited for an intervention study, as well as a control group. The majority of pharmacists in the control and active group considered ADR reporting a natural task for pharmacists, and had positive attitudes towards reporting adverse drug reactions

caused by OTC medicines. A majority had not reported ADRs to either regulatory agencies or the industry. A number of factors were cited as preventing pharmacists reporting: uncertainty if an ADR had occurred, lack of knowledge of reporting rules, a view that an ADR was well known, uncertainty about their role, lack of time and ADR form unavailability. Although a majority would contact a patient's physician in the case of a severe ADR, only a minority would have reported it. Granas et al argued that lack of awareness and understanding of the pharmacovigilance could be explained by the lack of pharmacovigilance taught at university and that strengthening of undergraduate education was required. After an educational day and three-month study period, the active group became far more confident about ADR reporting than the control group.

An Australian study found that hospital pharmacists were more familiar with the ADR reporting than medical staff, and more likely to report²⁹⁷. One in four pharmacists were in favour of a fee for reporting ADRs. Seriousness of the ADR, unusualness of the ADR, and an ADR in a new product were factors that encouraged ADR reporting; as did confidence in the diagnosis of an ADR. Time was an inhibitor of reporting in 44% of cases, with well known, trivial or uncertain ADRs being perceived as less important to report.

A case-control study of pharmacists in Portugal (response rate 86.8%) found ADR reporting probability higher in hospital pharmacist compared to community pharmacists²⁹⁸. The following attitudes were found to have a major effect on the probability of ADRs being reported:

- Really serious ADRs are well documented by the time a drug is marketed.
- I would only report an ADR if I were sure that it was related to the use of a particular drug.
- It is only necessary to report serious or unexpected ADRs.
- I do not have time to think about the involvement of the drug or other causes in ADRs.

A study of pharmacists' attitudes towards ADR reporting in Hong Kong found that severe, unusual ADRs, and ADRs to new drugs were more likely to be reported²⁹⁹. Although over 90% of respondents felt ADR reporting was a professional duty, few had participated. They found no relationship between the length of practice, the location of practice, patient contact time.

Chapter 2 Research Methods

2.1. Introduction

This chapter sets out the overall study design, the rationale for the chosen methodologies, and describes in detail the methods used in each branch of research. The main areas dealt within this section are: the literature survey, self-completion questionnaires, a retrospective analysis of an adverse drug reaction database, and qualitative interviews.

2.2. Background to the overall study design and sequence

The present studies have been undertaken over an extended period of time, which has led to the chance to refocus the research onto matters arising during data analysis. The primary concern is with improving the reporting of ADRs to the Yellow Card scheme in the West Midlands region, although it is intended that the research will be of more general interest to improve adverse drug reaction reporting in the UK.

Owing to the researcher's personal interest in the reporting of ADRs, the initial research focus was on supporting hospital pharmacist ADR reporting, which had commenced in 1997. Subsequently, it became apparent that other researchers were conducting research into factors that might influence individual hospital pharmacist reporting. Consequently, work was concentrated upon two other issues that may impact on the role of hospital pharmacist reporting. These were:

- The educational focus at undergraduate level on the Yellow Card scheme.
- The managerial focus of chief pharmacists on ADR reporting.

The first area (*vide supra*) was to be addressed through a postal survey focusing on the extent of teaching about the Yellow Card scheme in schools of pharmacy, and for comparative purposes in schools of medicine. The second area was chosen, since pharmacy departmental

policies and manager resource allocation could impact on hospital pharmacists' professional activity and hence influence their ability to report. It was decided to survey chief pharmacists' attitudes towards ADR reporting. Since both heads of schools of medicine and pharmacy, and chief pharmacists' time is constrained, and since both groups are geographically widely spread throughout the United Kingdom, a survey methodology was deemed most appropriate.

A concurrent research focus was a retrospective analysis of the ADR reports received by the West Midlands YCC. The result of this analysis, described in chapter 5, dictated that the research direction change towards GP ADR reporting rates, which were falling in absolute terms. In comparison, ADR reporting rates of other professional groups new to this role, including hospital pharmacists, were either increasing or stable.

Previous research of GP attitudes to ADR reporting in the UK had been based on theoretical ideas of reporter behaviour not grounded in the real world. Acknowledging the limitations of previous research, and the continually evolving practice environment of the general practitioner, which has also undergone several important changes throughout the intervening years, it was felt important to re-visit GP views on ADR reporting at a more fundamental level. For this reason a qualitative approach, grounded theory, was chosen.

2.3. *Literature review*

A review of the literature was undertaken to identify relevant research papers and professional publications. Although hospital pharmacist reporting was the initial research interest, searches were deliberately focused on attitudes to adverse drug reactions within any health professional group – since such information may shed light on other professionals reporting habits, and also could be used for comparative purposes.

A number of databases were used for the initial literature search.

Medline (Ovid)

Medline was searched using the following MESH terms, chosen because of their relevance to the subject area.

Adverse Drug Reaction Reporting Systems,

Drug toxicity, and

Product surveillance, postmarketing.

Boolean search terms were used in combination with MESH terms physicians and pharmacists in order to narrow the search to those articles contained with the professionals' reporting of adverse reactions. Wild card searches were also used.

Individual author searches were conducted, where such authors had an obvious key role within the research area. Key papers were also analysed for papers they cited, and relevant papers were obtained. In 2002, Aston University's Ovid subscription was discontinued and incremental search strategies were therefore replicated at Pub Med, hosted by the US National Library of Medicine (<http://www.ncbi.nlm.nih.gov>).

Pharmline

Pharmline was searched using the Thesaurus terms: Post Marketing Surveillance and Adverse Reaction Reporting.

ISI Web of Science

The ISI Web of Science was used to search for Adverse Drug Reaction Reporting Systems, Drug toxicity, and post-marketing surveillance. The citation tracking

function was used to relevant identify papers citing key papers concerned with the involvement of healthcare professionals in spontaneous reporting.

Ongoing literature retrieval processes

Given the time period over which this research programme was undertaken, it was important that literature searches were repeated, and kept up to date.

Some ongoing search strategies were developed. Searches on *Pub Med*, *World of Science*, and *Pharmline* were saved and conducted on a regular basis in order to incrementally update references.

Hand searches of key journals were undertaken, such as *The International Journal of Pharmacy Practice*, *Drug Safety*, *Pharmacoepidemiology and Drug Safety*, and *The British Journal of Clinical Pharmacology*. Monitoring of the literature in the major health journals such as *JAMA*, *The Lancet*, *BMJ* and *Reactions*, a weekly adverse drug reactions abstraction service, was also performed.

As part of the researcher's job, awareness was also maintained of other relevant information sources, such as drug regulators' websites, the lay press, parliamentary publications, and professional bodies' websites. In addition, the researcher maintained an active interest in the field professionally, by contributing articles on ADRs and drug safety to a number of publications, publication of book chapters and attending key conferences on drug safety, such as the International Society of Pharmacoepidemiology Conference and the International Society of Pharmacovigilance annual meeting. See Appendix II.

Primary papers were sourced from Aston University, University of Birmingham, and Sandwell and West Birmingham NHS Trust postgraduate library. Papers were also obtained using inter-library requests, the internet sites such as Science Direct and Ingenta Connect, the National Electronic Library for Health and a visit to the British Library.

2.4. Research methods

Methods used in the present study, included self-completion questionnaire surveys, a retrospective analysis of a large relationship database held by the West Midlands YCC, and a qualitative study using semi-structured interview techniques and grounded theory.

2.4.1. Self-completion questionnaires

Surveys are a ubiquitous form of research within health service sector practice research. They can be carried out as self-completion postal questionnaires, face-to-face questionnaires, performed over the telephone, or increasingly by the use of internet survey tools. Although telephone surveys are good for geographically dispersed populations, they require greater resources than postal surveys. In the case of professional groups, with busy schedules, obtaining a convenient time for interview increases the difficulty of this method. Therefore self-completion questionnaires were chosen for both surveys undertaken as part of this research programme. In addition, the relatively large number of chief pharmacists, spread over a large geographical area, in UK NHS hospital trusts meant that a self-completion questionnaire was the most appropriate choice.

Self-completion questionnaire surveys are quantitative in nature, providing reliable data, if carried out correctly, for descriptive, and statistical analysis. However, it has also been suggested that surveys can obtain a false legitimacy because of the quantitative nature of the data they obtain³⁰⁰.

The legitimacy of the survey method is dependent on the reliability of the survey tool used and this in turn is affected by respondent behaviour. Respondents may be unwilling to provide confidential information, or unable to provide information (owing to a failure to remember key facts). Replies may owe more to a mixture of politeness, boredom and a desire to be seen in a good light, rather than a real exposure of true feelings, beliefs or behaviour³⁰⁰. These factors can undermine the reliability and validity of questionnaires.

The trustworthiness of the data therefore depends on the technical proficiency of the researcher. The use of incomprehensible or ambiguous questions reduces the reliability of the survey data. This is termed a failure of internal validity of the questionnaire.

The other criticism that surveys are open to is that their results do not represent the views of the wider population. If the sample obtained is not representative of the population, then this provides a failure of external validity. Samples from populations should be taken of such size that results can be considered representative of a wider population. Therefore, obtaining a sufficiently high response rate is important for the validity of survey methodologies. However, high response rates can be difficult to obtain, particularly in postal surveys.

Failure of external validity on this basis makes questionnaires prone to bias at low response rate. This is known as respondent bias. Since characteristics of non-respondents are unknown, the representativeness of the sample cannot be known. Success of over 50% is considered by some to be indicative of a successful survey instrument.

Another failure of external validity is when one generalises about what someone may say in a survey compared to his or her actual behaviour. The lack of a relationship between what a respondent says and what they do has been documented³⁰⁰. Therefore claims about actual behaviour should be limited from surveys dealing with attitudes of respondents, rather than markers of respondent activity.

It is important to note that structured self-completion questionnaires provide little opportunity to follow-up responses or to address ambiguities that survey participants may experience. Questionnaires may expose surface elements such as demographic information or questions about the provision of services, but provide little depth of analysis of underlying concerns and views. The use of attitudinal scales may allow some examine of deeper held views and

feelings about issues³⁰¹. Table 2-1 sets out some of the advantages of self-completion questionnaires compiled from Robson³⁰⁰ and Taylor and Walker³⁰¹.

Table 2-1 : Advantages and disadvantages of self-completion questionnaires

Advantages
Reduction of interviewer bias owing to standardised questions
High reliability after piloting
Provide useful background information
Convenience to the respondent
Low administration costs
Can be administered to many people simultaneously.
Allows time for respondents to obtain information.
Allow anonymity and frankness
Simple and straightforward approach to the study of attitudes, values, beliefs and motives.
Can obtain information from any population
Provide a good level of data standardisation
Often the only way to obtain large amounts of data at a low cost.
Disadvantages
Low response rates, especially in busy professional groups
Require an accurate mailing list
Reasons for non-responses to questions may be avoided without explanation
Ambiguities and misunderstandings of research questions may not be detected
Recipients may not like them
Non-returns require follow-up to ensure an appropriate sample
Relatively superficial information is obtained
Respondents may not take the exercise seriously, and this may escape detection

For study success, in terms of validity and reliability, the design of a questionnaire is crucial. Poor design discourages respondent participation. One method of obtaining richer data, which gives a quantitative measure of individuals' attitudes, is the use of attitudinal scales to indicate a respondent's views on particular statements. Attitudinal scales also have a number of advantages and disadvantages^{300,301} which are set out in Table 2-2.

Table 2-2 : Advantages and disadvantages of attitudinal scales in surveys

Advantages

Sometimes indicate how people will behave.
Allow the researcher to probe beneath the surface issues.
Provide numerical data.
Reliable.
Can be administered to multiple participants.

Disadvantages

Influenced by context.
Do always act as constant indicators of behaviour.

One of the main attitudinal scales is the Likert scale. These are generally configured with either a four-point scale or a five-point scale. Use of a four-point scale has been criticised for forcing respondents to provide an opinion, when they may not have one. The use of a five-point scale, including a middle neutral response, has been criticised since it may encourage a non-committal response³⁰¹. The counter argument to this is that it allows an additional graduation of opinion, and non-committal behaviour, or views, is also common outside of surveys.

2.4.2. Design and administration of self-completion questionnaires

As previously noted, the design of a questionnaire is crucial in order to maintain a high validity and reliability of the research instrument. Robson³⁰⁰ has listed a number of key factors that may help with securing a good response rate, see Table 2-3.

Table 2-3 : Factors that may improve response rates to self-completion questionnaires

Appearance - Easy to complete, with plenty of space for questions and answers
Clear instructions
Content arranged to maximise respondent co-operation
Use of coloured sections
Use of tick boxes, rather than more confusing that circling options
Repetition of instructions if confusion is likely
Use sub-lettering to group questions
A graduation of sections with an easy lead-in, more difficult areas in the middle, and an interesting final section
Piloting
Thanking the respondent at the end
Printed labels.
First class postage.
Enclosing a stamped addressed envelope for return.
Avoiding December mailings.

A systematic review of randomised controlled trials of any methods to influence the response rate to postal questionnaires identified a number of successful strategies³⁰². These are set out in Table 2-4.

Table 2-4 : Published strategies found to be effective at improving response rates to postal questionnaires

Strategy	Odds Ratio (95% confidence interval)
Monetary incentive	2.02 (1.79 to 2.27)
Short Questionnaire	1.86 (1.55 to 2.24)
Personalised letter/questionnaire	1.16 (1.06 to 1.28)
Coloured ink	1.39 (1.16 to 1.67)
Recorded delivery	2.21 (1.51 to 3.25)
First class post	1.12 (1.02 to 1.23)
Stamped return envelopes	1.26 (1.13 to 1.41)
Warning of questionnaire	1.54 (1.24 to 1.92)
Follow-up contact	1.44 (1.22 to 1.70)
Second copy of questionnaire	1.41 (1.02 to 1.94)
Questionnaire of interest	2.44 (1.99 to 3.01)
University origin	1.31 (1.11 to 1.54)

Questionnaires containing questions asking for sensitive information were less likely to be returned (Odds ratio 0.92; 95% confidence interval 0.87 to 0.98).

Covering letters are an important method of improving response rates to questionnaires. They should concisely indicate the aim of the survey and convey its importance to a potential participant. Confidentiality of the survey should also be stressed. The letter should also be tailored to the particular audience, and the name of any sponsoring organisations should be given. Pre-survey letters, warning of the arrival of a questionnaire may increase the response rate.

Follow-up letters are important in increasing return rates, and should reiterate the original aim and importance of the survey. Some argue the follow-up should also convey disappointment and surprise at the non-response³⁰⁰. Follow-up letters should not give the impression that non-response is common. Provision of an additional copy of the questionnaire should be enclosed along with another stamped addressed envelope for the convenience of respondents. Providing a section upon which subjects may indicate why they have chosen not to participate may provide useful information, as well as potentially deterring some people from not responding.

2.4.3. Piloting self- completion questionnaires

The piloting of questionnaires and accompanying letters is essential prior to the wide scale distribution of a survey to main study recipients. The process evaluates the acceptability of the research instrument, and its internal validity, and allows an opportunity to expose alternative meanings and ambiguities contained within early drafts. Piloting allows an opportunity to make revisions of the questionnaire. Where possible questionnaires should be piloted in individuals who are of a similar nature to the intended respondents, or in those with prior experience of questionnaire design.

2.4.4. Self-completion postal questionnaires employed in this research

The following describes in further detail the two self-completion postal questionnaires used in this research. Common components are described below.

Design of questionnaires

Questionnaires used in the present study were designed by first brainstorming issues to be covered by the questionnaire. This process was informed by previous work in the area uncovered by the literature review and the researcher's knowledge of the subject area. Following the initial brainstorming process issues were grouped into logical domains of interest and preliminary closed questions were formulated to address these topics.

A number of open questions were also composed in order to obtain information that could not be elucidated by closed questioning. Open-ended questions create additional work in terms of analysis as well as losing some of the reliability that structured questionnaire design imparts. Consequently, they were kept to a minimum.

The use of negative questions was avoided, as was the use of questions, which were ambiguous or contained more than one idea.

The groups of questions were then put into what the researcher considered a logical progression throughout the questionnaire. In an attempt to ensure questionnaires were as short as possible, questions underwent further review by the researcher to ensure they added benefit to the research instrument. A number of questions were deemed suitable for the use of attitudinal statements – with appropriate Likert scales attached.

Results analysis

Data was coded and entered in to the SPSS (SPSS for Windows, Rel. 12.0.1. 2003. Chicago: SPSS Inc.). Valid response rates have been used through the results section; these only

include analysis of responses to those questions actually answered in a returned questionnaire. Graphs have been produced using Excel (Microsoft® Excel ® 2004 for Mac) after extraction of data from SPSS (SPSS for Windows, Rel. 12.0.1. 2003. Chicago: SPSS Inc.).

Non-parametric statistical tests were applied to nominal data, where applicable. The continuity test for Pearson's chi-squared test (and Fisher's exact test for low frequency cells) was employed to investigate whether there was a statistical significant association between variables. A p value of ≤ 0.05 was regarded as indicative of a result with statistical significance.

The validity of the results is dependent on the respondents providing valid responses and it is possible that some respondents may provide falsely positive answers owing to fear of retribution or a desire to conform with a perceived professional consensus, even though confidentiality was assured.

2.4.5. Survey of chief pharmacists attitudes towards ADR Reporting

2.4.5.1. Aims

This questionnaire was designed to identify issues related to the reporting of ADRs by hospital pharmacists within the UK. Heads of pharmacy services were focused on because although hospital pharmacists are individual professionals, they operate within a centralised service, which is subject to management allocation of resources and priorities. This allocation of resources varies on the basis of perceived organisational needs or priorities within the NHS trust. The culture and leadership of a pharmacy department may also influence the priority given to the Yellow Card scheme.

The aims were:

- To examine the prevalence and nature of local ADR reporting schemes within UK hospital pharmacy departments

- To examine problems related to ADR reporting by hospital pharmacists within UK hospitals
- To examine the views of the heads of pharmacy services within the UK with regard to ADR reporting

2.4.5.2. Design and piloting

Development of the questionnaire was informed by previous research concerned with hospital pharmacist reporting and brainstorming of potential issues involved as previously documented. The questionnaire was piloted on four chief pharmacists and four principal pharmacists responsible for clinical services. Questionnaires were also shown to Aston University staff with hospital managerial experience, as well as to experienced researchers.

The front cover included both the Aston University Pharmacy Practice Logo in addition to The West Midlands YCC logo. A tick box form was provided on the front cover allowing non-respondents to indicate their reasons for not doing so. Such a frontispiece may also prompt feelings of guilt leading to completion of the questionnaire.

The questionnaire consisted of four sections spread over four pages. Pages were numbered page 1 of 4 etc, in order that respondents would feel they were making progress. Some researchers suggest this can reduce the response rate.

The four sections were:

- About your trust (six questions)
- Benchmarking schemes (two questions)
- Local ADR Reporting Schemes (six questions)
- Your views on ADR reporting. (sixteen statements with attached Likert scale responses)

Demographic information was collected at the end of the questionnaire, and a section for open text responses was included. The term “*your trust*” was defined as the trust at which the respondent had managerial responsibilities. A copy of the questionnaire is in Appendix II.

2.4.5.3. Survey population

The population to be surveyed was chief pharmacists. Since it was logistically possible to mail all Acute NHS Trusts, the sample consisted of all cases in the population. Therefore no sample size calculation was carried out. The amended questionnaire was sent to all 209 acute NHS trusts in the UK, addressed to the chief pharmacist, with a covering letter and pre-paid return envelope in February 2002. Chief pharmacist was defined as the pharmacist with overall strategic control of the pharmacy service within the Trust. A tick box form was provided allowing non-respondents to indicate their reasons for not doing so. A second mailing was sent to 9 weeks later.

2.4.5.4. The survey

The survey was posted on the 7th of February 2002 (Thursday). A follow-up questionnaire was posted on the 9th of May 2002 (Thursday). The nine-week gap was chosen, since this was the point at which it was judged replies had ceased to arrive. All mailings contained a stamped-return envelope, and were mailed first class.

2.4.5.5. Accompanying letter.

An accompanying letter on West Midlands YCC headed paper explained to chief pharmacists the context the survey was taking place within. Participants were informed that the survey was not anonymous, but that the data would only be published as untraceable aggregated information, and that no information would be published that could be traced to individuals or institutions. A phone contact at Aston University was supplied.

As previously note, personal letters outlining University sponsorship is a strategy that can increase response rates to postal questionnaires. Appendix III contains a copy of the accompanying letter.

2.4.5.6. Data management

Questionnaires were coded and input into SPSS (SPSS for Windows, Rel. 12.0.1. 2003. Chicago: SPSS Inc.) as they were received. Following input of all data, the dataset was checked for outliers owing to potential data-entry errors.

2.4.5.7. Statistical analysis

Statistical analysis was performed using SPSS (SPSS for Windows, Rel. 12.0.1. 2003. Chicago: SPSS Inc.). Significance testing was performed using Pearson's χ^2 . For tables with a degree of freedom of one, Yates' Correction for Continuity was applied.

For tests comparing non-medical affiliated hospitals with medical affiliated hospitals, responses coded as "*Don't know*" (n=5) were excluded from the analysis to avoid low expected cell counts which would invalidate Pearson's χ^2 . Similarly, responses of "*Don't know*" in the questions about whether ADRs had been on the agenda of the Drug and Therapeutics committee and whether a local scheme for ADR reporting existed were also excluded on a similar basis.

For the purposes of statistical comparison, Likert scales were collapsed into three point scales using the recode function of SPSS (SPSS for Windows, Rel. 12.0.1. 2003. Chicago: SPSS Inc.) to avoid low expected cell counts.

2.4.6. Survey of head of medical and pharmacy schools

2.4.6.1. Aim

To discover the extent of teaching about the CSM's Yellow Card scheme and ADRs within the UK's schools of medicine and pharmacy.

2.4.6.2. Design

A self-completion, reply-paid questionnaire consisting of five closed questions, and two open questions was developed. The final questionnaire design is in Appendix IV.

2.4.6.3. Survey population

The final survey was mailed to all heads of undergraduate schools of medicine (n=26, including 2 new medical schools with their first intake in 2002) and pharmacy (n=16) within the UK.

2.4.6.4. Pilot

The questionnaire was piloted on teachers of undergraduates in pharmacy (two senior lecturers) and medicine (a senior lecturer and specialist registrar with teaching responsibilities related to clinical pharmacology).

2.4.6.5. The survey

The survey was posted on the 6th of September 2001. A reminder letter, the first follow-up, was posted on the 16th of November 2001. A final reminder, the second follow-up, was issued on January 25th 2002, along with a final telephone reminder a week later.

2.4.6.6. Accompanying letter

The accompanying letter, on West Midlands YCC headed paper, outlined the importance of the Yellow Card scheme, and the aim of the research being undertaken. The context the survey was taking place within was explained.

Participants were informed that the survey was not anonymous, but that the data would only be published in untraceable aggregated format. No information would be published that could be traced to individuals or institutions. A phone contact was supplied.

All mailings contained a stamped-return envelope, and were mailed first class. Appendix V contains a copy of the accompanying letter.

The medical and pharmacy questionnaires asked the same questions including:

- Number and specialisations of staff involved in teaching about ADRs.
- The inclusion of the Yellow Card scheme in the syllabus.
- The inclusion of the Yellow Card scheme in course assessments.

- Use of external speakers on practical aspects of the Yellow Card scheme.
- Usefulness of providing a guide to reporting, a yellow card and “*Current Problems in Pharmacovigilance*” to students.

In addition, an opportunity for open comments was provided at the end of the questionnaire.

2.4.6.7. Data management

Questionnaires were coded and input into SPSS as they were received. Following input of all data, the dataset was checked for outliers owing to potential data-entry errors.

2.4.6.8. Statistical analysis

Statistical analysis was performed using SPSS. Significance testing of survey data was performed using cross-tabulation using Pearson’s χ^2 . For tables with a degree of freedom of one, Yates’ Correction for Continuity was applied.

2.5. Retrospective analysis of ADR reporting in the West

Midlands

2.5.1. Aims

The aim of this analysis was to profile the demographics of the ADRs in the West Midlands region within both primary and tertiary care. The issues to be examined were:

- The reporting rates, and trends, for health professional ADR reporting
- Trends in reporting rates in the West Midlands in comparison to:
- National Yellow Card reporting rates.
- Trends in Health Episode Statistics (HES) for NHS hospitals.
- A more detailed analysis of reporting with NHS Acute trusts and NHS Primary Care Trusts during 2004-2006, examining the relationship between reporting rates and attributes of those organisations.

2.5.2. Description of the West Midlands YCC database.

The West Midlands YCC has collected ADR reports to the West Midlands region in a large Access (Microsoft) database since 1995. Reporting statistics have been published in its annual reports since 1993, although only partial data is available for 1993.

Details of case reports and reporter details are held in this relationship database, allowing detailed queries to be undertaken. The database is only partial, since reporters send a proportion of Yellow Cards directly to the MHRA (approximately 20%). These reports are termed bypass reports.

In April 2006, as an outcome of the *Report of an Independent Review of Access to the Yellow Card Scheme*¹⁵⁶, the West Midlands YCC ceased to collect ADR reports in an independent database. All Yellow Cards are now collected centrally by the MHRA. Only partial data is therefore available for the calendar year 2006, although data is available for the financial year 2005 to 2006.

2.5.3. Analysis of reporting trends within the West Midlands region: 1994-2005.

Data was extracted from the West Midlands YCC database for trends in professional reporting. Trends in the reporting of serious reactions and reports to black triangle drugs by professional groups were also examined by reference to annual reports published by the West Midlands YCC.

2.5.4. Comparison between West Midlands regional data and MHRA national data

National data on ADR reporting was obtained from the MHRA under a Freedom of Information Act (1998) request for comparative purposes.

2.5.5. Examination of Hospital Episode Statistics

Publicly available Hospital Episode Statistics (HES) were obtained from the HES online site (<http://www.hesonline.nhs.uk>). Trends in admissions related to ADRs were examined in two ways:

- An examination of primary ICD10 codes related to ADRs, as defined by Waller et al³⁰³
- An examination of secondary ICD 10 codes Y40 to Y59 (external contributing causes to admissions)

HES for primary ICD10 codes which could be related to prescribed medicines were extracted from online databases supplied by the HES-online service, using the list of ICD10 codes related to ADRs previously used by Waller et al³⁰³ in their examination of HES codes from 1996 to 2000. However, during a review of these codes, an additional code related to drug therapy was discovered which Waller had not included – *E24.2 Drug-induced Cushing's syndrome*. The full list of primary ICD codes is printed in appendix VI. Data was extracted from HES data tables to create a new table of ICD codes by year. Histograms were created to examine trends in both primary and secondary ICD codes.

2.5.6. West Midlands Acute NHS Hospital Trust reporting 2004 -2006

An analysis of West Midlands Acute NHS Hospital Trust ADR reports was undertaken from 2004 to 2006. Reports from 1st April 2004 to 31st of March 2006 were extracted from the West Midlands YCC database, including the Acute NHS Hospital Trust, the drug name, and the professional group of the reporter. Specialist NHS Trusts and Acute Mental Health Trusts were excluded from the analysis, since differences in patient characteristics, patient activity, drug therapy choices made them unsuitable comparators.

The West Midlands YCC centre is based within an acute NHS hospital Trust. Early examination of data showed this trust's overall Yellow Card reporting rate per 100,000 admissions outperformed the next best performing trust by a factor of 4.3. As an obvious special cause for performance was identifiable, the decision was made to exclude that NHS trust from further statistical analysis since it would skew the data analysis by acting as an extreme outlier. Its results are used a comparator site when appropriate.

The data was extracted from the West Midlands YCC database was exported into Excel (Microsoft® Excel ® 2004 for Mac) and then combined with hospital admission statistics for the same period obtained from the HES online website (<http://www.hesonline.nhs.uk>).

Reporting rates were calculated as the number of Yellow Card reports per 100,000 admissions. Admission rates were chosen over another measure of patient activity, Consultant Episodes, for the following reason. Hospital inpatients are assigned to a consultant who is responsible for their treatment and their period of care under a consultant is termed a "Consultant Episode" (CE) , also known as a Finished Consultant Episode (FCE). In the majority of cases, just one consultant treats a patient during their stay in hospital. For these patients, there will be only one CE, and therefore only one HES record. However, in 5% of cases primary responsibility for a patient is transferred to another consultant and a new HES record is created. Therefore the total number of CEs will exceed the patients admitted to hospital. For that reason admissions were used as a measure of hospital activity.

As well as the number of reports per acute NHS trust, data was extracted from the West Midlands YCC database in order to analyse the spread of reporting in the professional groups.

2.5.6.1. Examination of Healthcare Commission medicine management indicators as indicator of Yellow Card activity.

Healthcare Commission 2005/6 Medicines Management Review data was obtained from the Healthcare Commission website (<http://www.healthcarecommission.org.uk>). Data related to acute NHS trusts in the West Midlands region was extracted from the Healthcare Commissions data tables and analysed within SPSS for any relationships between markers of medicine management performance and the hospital Yellow Card reporting rates per 100,000 admissions.

2.5.7. PCT reporting analysis 2004 to 2006

Data on PCT reporting rates were obtained from the West Midlands YCC database. All reports for from 1st April 2004 to 31st of March 2006 were extracted, including the PCT, the drug name, and the professional group of the reporter. Data was imported into Excel

(Microsoft® Excel ® 2004 for Mac) and pivot tables used to create tables of PCT Yellow Card reports, ordered lists of drug reports, and professional group.

Estimated PCT population data for 2004 based on projections from the 2001 census data was obtained from the West Midlands Public Health Observatory (<http://www.wmpho.org.uk>). The proportion of the population over the age of 65 years of age was calculated for each PCT. Deprivation index scores for PCT areas, published by the Office of the Deputy Prime Minister in 2004, were obtained from the *National Primary Care database's* website (<http://www.primary-care-db.org.uk>).

Quality and Outcomes Framework (QOF) performance information for PCTs was obtained from the NHS Information Service website (<http://www.ic.nhs.uk>). QOF data for 2005-2006 was used for analysis, on the basis that it would be more likely to reflect performance, since GP practices would have overcome initial teething problems relating to the implementation of the new contract.

Statistics on the GP workforce within the West Midlands region were requested and obtained from the *NHS Information Centre* at Leeds. Data for each PCT included: the proportion of GPs over 55 years of age, the proportion of female GPs, the average list size and the proportion of GPs in single-handed practice.

The top ten reported drugs received by the West Midlands YCC for 2004-2005 and 2005-2006 were calculated. Vaccines and drugs that required specialist administration in hospitals were excluded from the analysis. The two top ten lists were then combined to create a group of "top drugs" for the 2004-2006 period. Data on prescribing for these drugs within West Midlands PCTs were obtained from the *NHS Information Centre* in Leeds for the 1st April 2004 to 31st of March 2006 period. The total amount of prescribed items was also obtained for each year.

For the thirty PCTS an Excel (Microsoft® Excel ® 2004 for Mac) spreadsheet was created holding all the above information, which was then imported into SPSS (SPSS for Windows, Rel. 12.0.1. 2003. Chicago: SPSS Inc.).

Statistical tests

Each variable was then tested for skewness and kurtosis. Z_{skewness} of above 2.58 and Z_{kurtosis} above 2.58 (significant at $p < 0.01$) was treated as indicative of non-parametric data from a non-normal distribution.

Skewed data was transformed using the compute function of SPSS (SPSS for Windows, Rel. 12.0.1. 2003. Chicago: SPSS Inc.), using square root transformation. An additional +2 was used when zero values were involved.

Since measures of skewness and kurtosis only measure one aspect of normality each, the Kolmogorov-Smirnov test was performed on variables, and transformed variables, to test if the distribution as a whole deviated from a normal distribution. Variables, and transformed variables, were noted to be parametric if they exhibited threshold values of Z_{skewness} and Z_{kurtosis} below 2.58 ($p < 0.01$) and non-significant ($p > .05$) Kolmogorov-Smirnov test results.

Correlations were then performed to examine associations between PCT characteristics and Yellow Card reporting rates. Where parametric data was available, scatterplots were created using SPSS (SPSS for Windows, Rel. 12.0.1. 2003. Chicago: SPSS Inc.), and the Pearson correlation co-efficient was used. R^2 values were also calculated. Trend lines were included on scatter plot graphs showing parametric data. For Pearson's correlations undertaken using transformed data, Spearman's correlation was also undertaken on the untransformed data for completeness.

To explore correlations that involved data that had violated parametric assumptions (i.e. non-parametric data) Spearman's correlation co-efficient, r_s , was used. No trend line was placed on scatter plots involving non-parametric data.

2.6. *Qualitative study of general practitioner attitudes towards the Yellow Card scheme*

2.6.1. Aims

The fall in GP reporting highlighted during the retrospective review of ADR reporting within the West Midlands led to interest in possible reasons why GP ADR reporting was falling within the West Midlands (and within the rest of the UK). The GP practice environment has undergone significant change in the ten years that had passed since previous research had been performed. A qualitative approach was therefore chosen to investigate GPs' attitudes towards the Yellow Card scheme. This study had three main objectives:

- To investigate the views of general practitioners towards the Yellow Card Scheme
- To identify potential barriers to Yellow Card reporting
- To identify motivating factors for Yellow Card reporting
- To develop a theoretical framework to explain general practitioners' involvement in the Yellow Card scheme

2.6.2. Rationale for choice of method

Little contemporary research exists of GP attitudes in the United Kingdom, and much of the previous research in the UK has focused on postal questionnaires. A qualitative method was therefore chosen to elucidate new information about GPs' involvement with the Yellow Card scheme.

2.6.3. Qualitative methodology

Qualitative research tends to work with small amounts of data in comparison to quantitative research³⁰⁴. The broad generalizability of research is sacrificed in order to concentrate on richness and detail of research subjects' understandings and interaction with systems and the

environment/culture they operate within. Qualitative data works with a relatively small number of cases, sacrificing scope for detail³⁰⁰. Qualitative methods can provide ‘deeper’ understanding of social phenomena than quantitative research instruments, especially in areas where little information exists.

Health service researchers have been critical of qualitative methods, which has not been helped by some of the rhetoric used by post-modernist sociologists where prior social or political agendas and stances are merely rubberstamped, rather than any real attempt to create an intellectual or objective view of social relations.³⁰⁵ However, the use of qualitative research methods has become increasingly common in general practice research³⁰⁶⁻³¹³.

2.6.4. Population and sampling method

Since qualitative research seeks to reflect diversity within a population, and does not aspire to statistical generalizability or representativeness³⁰⁴, the study was designed to reflect the views, opinions and experiences of GPs with varying levels of engagement who fell within the operational area of the West Midlands YCC. Research was therefore carried out in general practitioners surgeries throughout Shropshire & Staffordshire SHA, Birmingham & the Black Country SHA, and West Midlands South SHA between April 2006 and March 2007.

A purposive sampling method was chosen, which enabled the researcher to obtain qualitative data that will allow varied perspectives and deviant case analysis. More strictly grounded sampling methods used in qualitative research, where specific cases are sought out on the basis of early analysis of interviews, was problematic given the necessity of supplying a plan to an ethics committee. In addition, as the West Midlands YCC was able to identify different GPs who were reporters to the Yellow Card scheme, this sampling method had the advantage of ensuring that the views of reporters were canvassed.

The researcher planned to recruit thirty general practitioners from three groups:

Regular reporters to the Yellow Card scheme, defined as GPs who have reported more than once in the last year and least once in the previous year .

Lapsed reporters. Defined as GPs who have not submitted a Yellow Card in the past 12 months, who are still within the population, but who have previously reported in the past 5 years.

Non-reporters. Defined as GPs who are working within the population for whom there is no record of a Yellow Card report.

Within each of the three groups an attempt was made to a balance for the geographical spread of the region.

2.6.5. Exclusion criteria

The study had two exclusion criteria:

- Non-reporting GPs new to the operational area of the West Midlands YCC, (defined as arriving in the past 12 months) since they may have been regular reporters to the Yellow Card Scheme.
- Declining to be interviewed.

2.6.6. Recruitment and management of the interview

The researcher contacted GPs by use of a letter (Appendix VII), which explained the purpose of the study. GPs were asked to indicate their willingness to participate by use of a tear-off reply slip pre-paid return envelope, email, text message or by a phone call. The letter also included an information leaflet (Appendix VIII). After a GP agreed to participate, the researcher arranged a time and place for convenient for the GP to be interviewed.

On attendance at the interview, the researcher asked the participant if they had read the information sheet, and supplied a replacement information sheet if they had lost the original. The participants were then invited to sign a consent form for the study. Subjects were invited to ask any questions about the nature of the study and any concerns they have before signing the consent form.

Subjects could decline to be interviewed at any point, up to and including during, the interview. In addition, subjects could withdraw their participation from the study for one

week following the interview. In this event, any recordings or transcripts of the interview were to be destroyed by the researcher.

Participants were assigned a unique reference number at the interview, and all interview recordings and transcripts were labelled with this unique code. Interviews were recorded on mini-disc, using a small and discrete recording device and microphone. Recording was chosen, since note-taking can interfere with the interview process³¹⁴, and details of interviews can be missed leading to failure of the coding process to identify all conceptual categories that existed in the interview.

At the end of the interview process participants were thanked for their time, and were offered the chance to listen to the recording in private with the option of erasing the contents. They were also reminded of their right to withdrawn from participation in the study by placing a phone call to the researcher.

2.6.7. Defining grounded theory

Grounded theory was developed in the late 1960s by Barney Glaser and Anslem Strauss, and formally introduced in the text *The Discovery of Grounded Theory*³¹⁵. It was developed as a systematic method of generating theory from data; the theory being “grounded” in the collected data. Grounded theory develops theories from research grounded in data, rather than deducing testable hypotheses from existing theories³¹⁶. Grounded theory key concepts include concepts, coding and codes.

At the time of Glaser and Strauss’ research, qualitative research in sociological research was out of favour and sophisticated quantitative methods had become popular. The scientific method involving systematic observation, reproducible experiments, and logically deduced hypotheses for testing had made positivism the dominant paradigm in sociology in the 1960s³¹⁶. Glaser and Strauss’s development of grounded theory contested this paradigm of quantitative research by offering systematic strategies for qualitative research practice. They

argued that systematic qualitative research contained its own logic and could be used to generate theory grounded within the data.

In later elaborations of grounded theory, Glaser and Strauss developed alternative schools of thought. The Straussian paradigm of grounded theory became very heavily concerned with the validity of the research and imposed a systematic approach to examining the data, while Glaser focused on what could be considered a more qualitative paradigm. Glaser was in favour of flexibility in the approach to grounded theory, with theories about social phenomena naturally emerging from the analysis. He considered the rules and procedures developed by Strauss time-consuming and confusing, and more an attempt to replicate, or ape, the scientific model by including such concepts as generalizability, precision, and verification.

Glaser argued against any literature review before undertaking research, suggesting such activity would desensitise the researcher by exposing him or her to borrowed concepts. Previously published material was only to be used late in the research process, in order to make comparisons with the researcher's findings.

Glaser was also against the taping of interviews, considering it counter-productive and an inhibitor of initial data analysis. He placed an emphasis on the use of field-notes to generate emergent concepts. Glaser also advocated an avoidance of discussion about the research, which was argued to reduce motivation, and impinge on the drive to develop concepts and theory; positive feedback making the researcher content, negative feedback hampering the individual's confidence to generate theory. However, despite Glaser's commitment to flexibility, he held rigid views towards, and was dismissive of, differing paradigms of grounded theory³¹⁷. Although there have been attempts to reconcile the two approaches to grounded theory, it is important to define which paradigm, or elements, of each grounded theory is being used in any research project. The term grounded theory is so wide in

interpretation, that its use without further clarification of the paradigm being employed is meaningless.

The present researcher comes from a scientific background, with a strong positivist approach. After examination of the characteristics of both approaches, it was decided to undertake the use of the Straussian model of grounded theory, as defined in the Strauss and Corbin's *Basics of Qualitative Research*³¹⁸. However, although the researcher did broadly follow the procedures and recommendations of Strauss and Corbin, his approach was tempered with the realisation that the researcher would naturally begin to develop a feel for emergent themes and issues outside of the formal coding system.

Charmaz³¹⁶ has listed the defining characteristics of grounded theory as:

- Simultaneous data collection and analysis
- Development of analytic codes and categories from data, rather than preconceived logically deduced hypotheses.
- Constant comparisons of cases within each stage of the analysis.
- Advancing theory development during data collection and analysis.
- The use of memos to elaborate on categories, specifying their properties and the relationships between them, and identifying gaps.
- Sampling strategies aimed towards building theory, rather than attempting to produce population representativeness.
- Undertaking the literature review of the area after an independent analysis.

Hypotheses are not formed in advance. Hypotheses are retrospectively formulated in order to try and explain the data.

It is important to note that grounded theory is not a merely a descriptive methodology. It is concerned with generating concepts that explain people's actions. Descriptive elements of grounded theory are used to illustrate emergent concepts. The results of grounded theory are not a reporting of facts, but a set of probability statements about the relationship between concepts or hypotheses developed from the empirical data of a study. Validity is therefore not

a key issue; grounded theory is judged on the basis of fit, relevance, workability and modifiability.

Fit: how concepts fit with incidents they are representing, measured by how thoroughly the method of constant comparison was done.

Relevance: how it deals with real concern of participants.

Workability: The theory works when it explains the problem with much variability.

Modifiability: can be altered when new relevant data is compared to existing data. A grounded theory is never wrong, it just has more or less fit, workability and modifiability.

There have been concerns about the use of grounded theory as a “bumper sticker” used to give academic respectability to qualitative research, rather than being used as a real description of the research process. Barbour has argued that few grounded theory papers discover surprising material and tend to have an uncanny resemblance to debates and concerns within the existing literature³¹⁹. It is argued that most researchers therefore use a pragmatic variant of grounded theory (which is arguable what Strauss and Corbin’s approach is), which includes the development of new themes alongside those already present in the literature. Since the present researcher was already familiar with the research literature in this area, there was no alternative to undertaking this pragmatic approach to grounded theory.

Another complaint is that uncritical uptake of grounded theory can result in a near mystical theory that somehow emerges from the data without any explanation of the process undertaken³²⁰. Strauss’s more structured approach seemed to avoid this possibility.

Although the present study did not attempt to triangulate to improve internal validity of the research, in reality such attempts are difficult to undertake, and can undermine the very contribution that qualitative research can provide³²⁰. Data collected by different methods come in differing forms, and are difficult to directly compare. Therefore, triangulation was attempted by maintaining the internal validity within the study by careful coding and theory generation.

A review of published qualitative research in general practice raised concerns that finer details of research were unelaborated, and that the qualifications of the researcher were not made explicit³²¹. Without rigorous reporting of the research methods, it is difficult to appraise qualitative studies.

2.6.8. QSR N6 software and its use within grounded theory

After an interview had been transcribed into standard Word documents, the documents were formatted for importation into QSR N6 (QSR International, 2002), and converted into plain text documents. All interviews were imported into QSR N6 as they became available so that analysis and coding could be undertaken while the field interviews were continuing. QSR N6 is a highly developed textual analysis programme. It allows for the swift coding of text files, multiple memo writing and rapid retrieval of material.

The use of specialised computer software in qualitative analysis has become increasingly common, and the software does enable the management and coding of large amounts of text to be undertaken more easily than manual methods allow. However, during the study the researcher was aware that the use of computer software should be as a tool, and not a method of analysis itself.

2.6.9. Coding, categorisation and memo writing.

The researcher became familiar with the interview data through the transcription process, which involved repeated listening. This allowed the researcher to develop an awareness of key themes and ideas, by becoming immersed within the data.

The coding process was commenced as soon as the first interview was transcribed. Initial coding of the data was conducted using a line by line microanalysis to develop open codes. Many of the first open codes consisted of “a priori” codes that were largely of a descriptive nature, which developed in line with the original research aims and the topic guide. Such codes were also drawn from the researcher’s own knowledge. However, other codes were

more related to issues raised by participants, so called “in vivo” codes. “In vivo” codes capitalise on the unexpected data that can be provided from carrying out a grounded theory study³¹⁹.

Focused coding is another stage of coding described by Charmaz³¹⁶, in which earlier codes developed during interview analysis are used to sift through later data. Decisions were made about existing codes applicability to the data, and merging of codes was undertaken to develop codes that made the most sense to analyse the data. As the analysis progressed, and the coding structure became more focused and analytical in nature these codes were grouped into conceptual categories using the tree node structure of QSR N6. Eventually a series of theoretical categories were developed, that contained a series of open “a priori” and “in vivo” codes. QSR N6 also allowed a series of base data codes to be inserted, such as gender, and reporting group.

The final stage of coding was Axial coding, which is described by Strauss and Corbin³¹⁸. The initial act of coding “*fractures*” data into open codes and then categories. Axial coding is a method of bringing data back into a coherent whole, in order to describe the relationships between categories (and the codes within them) on a conceptual level. The researcher sought to look for such relationships between such categories in order to develop theory. However, the use of Axial coding can be considered cumbersome, adding a further level of time-consuming data analysis³¹⁶. The present researcher found that use of conceptual categories and extensive memo writing was adequate in order to develop relationships between the emergent themes.

Throughout the coding process extensive use of memos was used. Memo writing is a pivotal step between data collection and writing drafts³¹⁶. Memo writing is an analytical tool that allows quick analysis of data and coding. Memos were appended to individual transcripts, codes and categories. Early memos were descriptive in nature, describing the views of GPs,

later memos began to discuss potential theories and linkages between the emerging conceptual categories. An example of a memo in QSR N6 is given in Appendix IX.

QSR N6 also provides some useful tools for examining intersections of coding, by pulling sections of text where specific codes are found in combination (called insections). This was found to be of particular use when used to compare reporting, non-reporting, and lapsed reporting GPs coding. For example, all instances of non-reporting GPs views on the reporting criteria of the Yellow Card could easily be obtained, and studied separately from the other groups of reporters, before examining them as a whole. Again, memos were used to analyse the results of these intersections. This iterative process allowed feedback into the research process in order to allow emergent themes and theories to be used in the subsequent interviews.

The final stage of the analysis was the writing up of the research. Conceptual categories were used as headings for specific sections, and further refinement of the relationships between conceptual categories occurred during the writing process. The analysis and theory generation continued during the writing up stage of the thesis, as has been described by Charmaz³¹⁶, who wrote *"Writing demands more than mere reporting. Through writing and rewriting drafts, you bring out implicit arguments, provide their context, make links with extant literatures, critically examine your categories, present your analysis, and provide data that support your analytic arguments."*

Memos were used to supplement quotes from respondents in the final write-up. The use of quotes is susceptible to the accusation of anecdotalism, in which a few choice quotes are used to convince the reader, and the researcher, that their findings are genuine³⁰⁴. Therefore, the researcher has attempted to provide quotes, sometimes extended in order to provide context, that support the text and the development of theory, rather than using them as mere anecdotes.

In order to help the researcher examine the relationships between conceptual categories and codes, diagrams were created using Inspiration (Inspiration Software Inc. version 8.0b, 2006), which attempted to show the relationships between concepts.

2.6.10. The interview process

Although qualitative interviews do not follow a formal structure, such as that used in quantitative surveys, some form of structure is essential if the interview process is to address the area of research. Two main approaches exist, the semi-structured interview and the in-depth interview^{300,314}. In-depth interviews tend to cover one or two small areas, and start with broad questions, with further questions generated from in-interview analysis of the respondents' answers and through the use of probes and clarifying questions³²². Semi-structured interviews have a loose but more structured content, consisting of open-ended questions which define the area to be explored. A series of questions about the subject area are asked, with the ability of the interviewer to be able to clarify or probe the answers given by respondents. As interviews are continued, and emerging concepts arise from collected data, further questions may be added to the interview structure in order to explore new areas of importance to theory generation.

The skills of the researcher are important during the interview process and the interviewer did attend study courses on qualitative interviewing and also practised those skills with postgraduate students on a pharmacy diploma programme. The researcher's interview skills and confidence also developed through the research process.

Interviews followed a topic guide (Appendix X), which consisted of a series of standardised opening questions for all participants. The course of the interview was however influenced by the responses given, and by the interviewer, who used prompts, probes and context specific questions. Contemporaneous analysis of previous interviews lead to questions related to emergent themes in the data being added to the interview schedule.

2.6.11. Preparation of transcripts

Transcripts of interviews were prepared as soon as possible after the interview, to enable early analysis of themes arising, which then could be feed back into the interview process. Transcription was a slow and time-consuming process. After transcription into a standard word-processing package, the interviews were converted into text files and imported into QSR N6.

2.6.12. Maximising reliability and validity of data collected.

The researcher involved researcher (KW), with experience in qualitative work with GPs, and there was regular contact to ensure that data collection and analysis was performed to high standards of reliability and validity.

The following points were considered, to ensure that the data collected and the analysis of the data was reliable:

Researcher background: During the analysis of qualitative data, the researcher inevitably brought his own perspectives and prejudices. The researcher endeavoured to understand the perspective this may place on his interpretations of the data during his analysis. The professional background of a researcher can have an important effect on the research participants behaviour³²³. Interviews where the researcher is viewed as an expert on the subject area may lead to participants suspecting the researcher as making judgements on their responses, leading to bias³¹⁴.

Use of mini-disc recorder: This is to ensure that no data is lost at the stage of transcription and that all transcripts will accurately reflect the content of each interview.

Generation of full transcripts: Interviews were fully transcribed, further ensuring that no data is lost or manipulated at the stage of data collection and presentation.

2.6.12.1. Analysis

This analysis followed a clearly defined pathway, which can be examined by any person wishing to verify the methods used to analyse the data collected. The following points were considered to ensure the validity of the data collected and of the following analysis

Inter-rater reliability: A sample of nine transcripts from the three sampling groups were independently manually analysed by KW, who examined themes and categories

within the data, and commented on the emerging coding frame to ensure rigour in the analysis. Variations in coding were addressed in order to arrive at a consensus.

Deviant cases: There was a comprehensive search for elements in the data that appear to contradict emergent themes. This method is useful to refine an analysis until it can explain the majority of cases under scrutiny.

Fair dealing: The researcher aimed to include a wide variety of different perspectives in the participants sampled (partly produced by the purposeful sampling method adopted by the study). This ensured that one group is not presented as if it were the sole truth of the situation.

2.6.12.2. Research ethics

The researcher became familiar with *The British Sociological Society's Statement of Ethical Practice*³²⁴, which sets out in detail the issues surrounding the central relationship between the researcher and research participants, and potential problems with use of field research up to and including publication³²⁵. Qualitative research can lead to anxiety in participants and publication of research can potentially damage the reputation of participants, or their social or professional group.

Several risks of qualitative research have been identified³²⁵:

Anxiety and Distress: Qualitative research is by its nature probing, and seeks to find underlying reasons and context for participants' beliefs and actions. It may be that some lines of questions may provoke strong feelings or distress, and these cannot always be predicted, giving the open-ended nature of questioning and use of probes.

Exploitation: The potential exists for a "power relationship" existing between the researcher and the participant. When the request for an interview comes from a fellow health professional the participant may feel pressurised into agreeing to participate. They may also become confused as to the role of the researcher, perceiving the interview as a test rather than an exploratory study. The professional background of the researcher was therefore made clear to participants in both the introductory letter, and before the interview process began.

Misrepresentation: The analysis of qualitative research is inevitably influenced by the theoretical framework, personal characteristics and preconceptions brought to the study by the researcher. Even allowing for the use of a qualitative research method that seeks to produce reliability within the research, subjective interpretations are created. Generalisations made as individuals' views are interpreted and placed in context with other participants views can lead to participants feeling they have lost control of their "identity" as expressed during the interview process. Interpretations of participants' actions may differ from the participants own views. One mechanism of reducing the risk of misrepresentation is to look for respondent validation, by making feedback to research participants' part of the research process. However, responses to

this approach are also open to interpretation, and can be considered harassment³²⁵. Additionally, such approaches can lead to researchers abandoning their own theoretical interpretations, and accept participants at face value³²⁰. Another approach is for the researcher to be aware of their own biases, which was the approach taken in the present study.

Identification of the participant: Qualitative research collects large amounts of information about research participants' views. The identification of a participant may lead to social harm or loss of professional reputation. Even with anonymized transcripts of interview, sufficient clues to identity can be revealed about their employment, geographical area, employment details or education may allow identification by third parties.

All participants remained anonymous and were not identifiable from the data, including removal of material from interviewee quotes that gave details of a participants' education, country of origin in the case of overseas doctors, or other data that could conceivably be used to identify the participants. Participants were only identified by their unique reference code. The reference sheet of codes and named individuals was stored separately from the data, and tapes were kept in a locked filing cabinet in a secure area of Aston University.

The researcher was cognisant of the need for confidentiality. This point was borne in mind when considering the future publication of material from the study and during the preparation of this manuscript.

2.6.13. Ethics application and research governance.

Ethical approval was obtained from South Birmingham Research Ethics Committee (a Multi-centre Research Ethics Committee -MREC). An application was made via the COREC (Central Office for Research Ethics Committees) website. The application was received by the MREC on the 13th of October 2005 (Reference number 05/Q2707/362). The researcher attended a meeting of the MREC on the 8th of November 2005.

The ethics committee gave provisional approval of the study on the 15th of November 2005.

The committee asked for a number of points to be clarified:

1. How participants would be identified.

2. The estimated length of the interview.
3. When recordings would be destroyed. The ethics committee being of the opinion that the recordings should be destroyed immediately following transcription.
4. Extension of the period during which the participant could withdraw from the study – up to and including before publication of the results.
5. A clarification of the sampling method. The researcher re-iterated his sampling method, pointing out that the sample was not seeking representativeness as it was a qualitative study.
6. A commitment to include the information letter with the initial invitation letter. Originally it was planned to supply this at the interview when consent was obtained.
7. A number of small changes to the information leaflet.
8. Some changes to the invitation letter and initial reply slip.
9. Explicit mention of the recording of the interview on the consent slip (Appendix XI).

Following submission of a letter clarifying these points, final approval of the study was given on the 2nd of December 2005.

Once ethical approval had been obtained from the MREC, Research and Development approval was sought from the 30 PCTs within the West Midlands region. This process took between 1 week and 12 weeks (average 6 weeks) depending on the PCT involved.

Chapter 3 Survey of NHS secondary care chief pharmacists' attitudes to Yellow Card reporting

The aim of this part of the present study was to evaluate the views of chief pharmacists on hospital pharmacists' role in adverse drug reaction reporting. It was also intended to investigate the possible pressures that that may affect the priority given to adverse drug reaction reporting within NHS Hospital Trusts.

The objectives of this part of the study were to:

- Obtain baseline data on the chief pharmacists and their NHS trusts.
- Identify key characteristics of the NHS Hospital Trusts in relation to ADR reporting.
- Identify the nature and extent of local ADR reporting schemes – and any future potential for such schemes.
- Determine any negative effects of hospital pharmacist ADR reporting, as assessed by complaints by hospital consultant physicians or patients about hospital pharmacist activity in ADR reporting.
- Investigate the attitudes of chief pharmacists to ADR reporting.

The results from the present section were obtained using a self-completion questionnaire "*Adverse Drug Reactions: Questionnaire of UK Chief Pharmacists*" which was mailed to all Chief Pharmacists (n=209) at NHS Hospital Trusts in the UK. A copy of the questionnaire is included in Appendix III.

3.1. Results

3.1.1. Response rate

The questionnaire had a response rate of 66% (137 out of 209) after the 1st mailing and which rose to 82% (172 out of 209) following the second mailing. Eighteen declined to participate, leaving 154 valid completed questionnaires (74% of questionnaires sent). This shows the questionnaire had good external validity.

3.1.2. Reason for non-completion

Fifteen respondents returned the questionnaire with a reason for non-completion. The reasons given are noted in Table 3-1

Table 3-1 : Reasons for non-completion of the Chief Pharmacists' questionnaire

Reasons given for non-completion	Number
Lack of time (including "too long", "unimportant")	7
Other reasons (including "No Pharmacy department", "Trusts merged" and "Trust no longer exists")	3
No Chief Pharmacist	2
Sensitive information	1
Never complete questionnaires	1
Addressee gone away	1

3.1.3. Nature of the respondents

Out of the valid 154 responses, the majority appeared to have been completed by chief pharmacists, with twelve passed on to other members of pharmacy management for completion. Analysis of those remaining 142 questionnaires shows the mean number of years the chief pharmacists had been in post was 8 years (range 10 weeks to 27 years). The mean number of years on RPSGB's professional register was 22 years (range 9 to 38 years). Fifty-eight percent of the chief pharmacists were male.

3.1.4. Reported nature of the survey hospitals

To the question "*Is your trust affiliated to a Medical School*", 44% (n=68) of respondents answered "*Yes*", 51% (n=79) "*No*", 5 (3%) "*Don't know*", with two missing values. Those answering with "*Don't know*" were excluded from further analysis, which compared NHS hospitals with medical school affiliations to those without.

The overwhelming majority of respondents, 99% (n=152), noted that they had a medicines management control device, such as a Drug and Therapeutics Committee (DTC) operating within the trust.

A minority (27%) of respondents reported that ADR reporting had been on the agenda of one of their medicine management control devices in the two years previous to receiving the questionnaire. Sixty-six percent said “No”. Seven percent did not know.

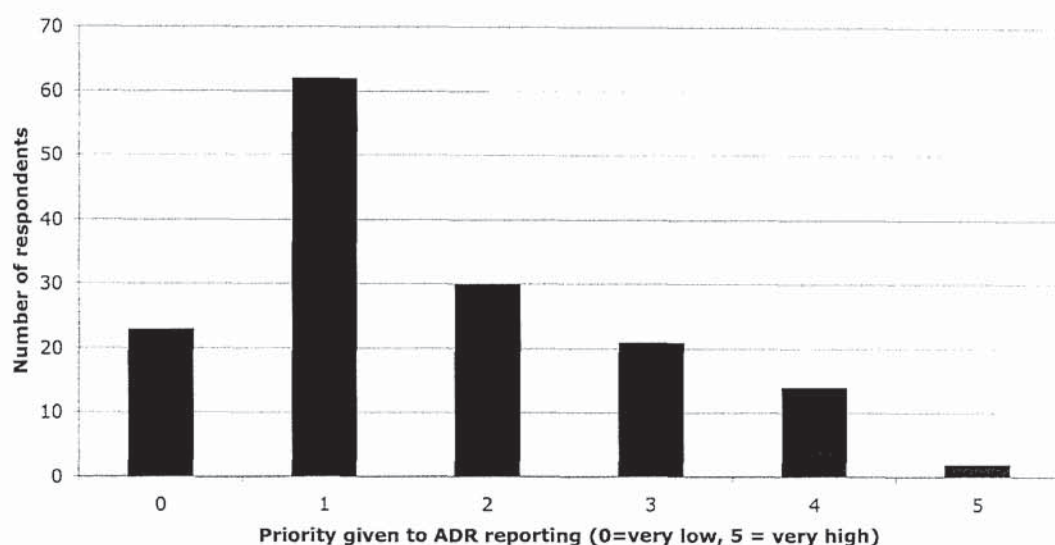
Hospitals where the chief pharmacist had noted an affiliation to a medical school were statistically more likely to have discussed ADR reporting on the agenda of a medical management control device, such as a DTC (Pearson $\chi^2=5.219$, df=1, P=0.022, Odds Ratio 2.36).

When asked “*Is there a member of medical staff who takes a lead in ADR reporting*” only 4 respondents (3%) replied yes, with 128 (83%) stating no. Fourteen percent (n=22) did not know if there was a member of medical staff with an interest in this area. In those trusts where a lead member of medical staff with a strong interest in ADR reporting, this interest was manifested in the form of meetings concerning ADRs (2 sites) and news bulletins about ADRs (2 sites).

3.1.5. Priority given to ADR reporting

When asked to rate the priority given to ADRs on a six point scale (0 to 5) by medicine management control devices within trusts, respondents gave a range of results. These results are depicted in Figure 3-1. There was no statistical association between medical school affiliated NHS hospital trusts and the reported priority given to ADR reporting by medicine management control devices.

Figure 3-1 : Priority given to adverse drug reaction reporting by NHS Hospital Medicines Management Control Devices



3.1.6. Benchmarking schemes

A small majority of respondents 32% (n=54) noted they were members of a national benchmarking scheme; with only five (3%) stating that ADR reporting rates were collected as part of the scheme.

A third of respondents noted they were members of a local benchmarking scheme, 18% of which (n=6) reported that the ADR reporting rate was measured by the scheme.

3.1.7. Local reporting scheme.

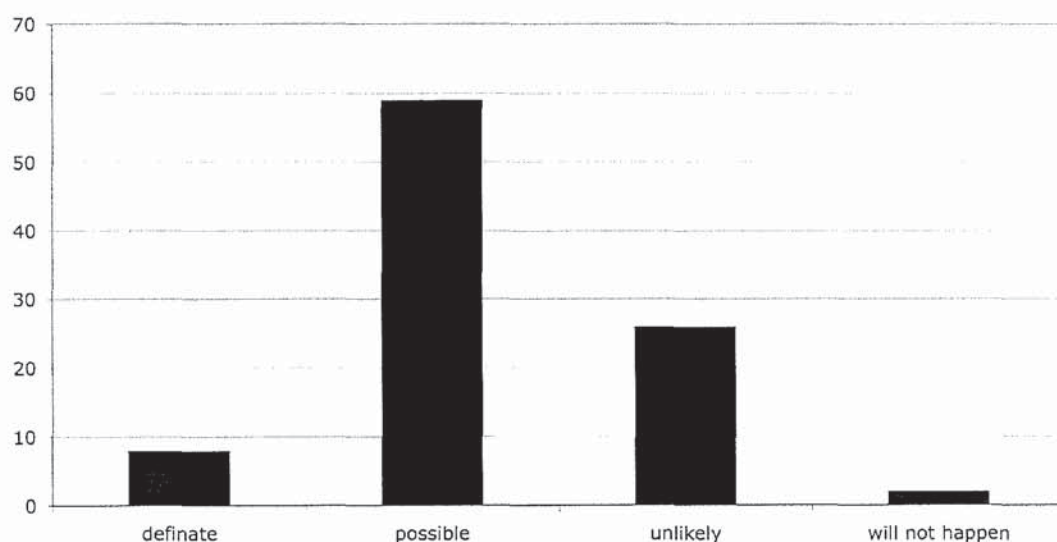
When asked “Does your trust have a local scheme for adverse drug reaction reporting?” 37% (n=56) responded positively. The majority responded with no, 61% (n=94), and 2% (3) did not know if a local scheme was in operation. (n=153)

Hospitals where the chief pharmacist had noted an affiliation to a medical school were statistically more likely to have a local ADR scheme (Pearson $\chi^2=5.1713$, df=1, P=0.017, Odds Ratio 2.29), compared to hospitals where no affiliation to a medical school had been noted.

Local schemes were targeted at medical staff 32% (n=50), nursing staff 25% (n=39), pharmacists 12% (n=19), professions allied to medicine 10% (n=16), and patients 4% (n=7). Three respondents noted their ADR reporting scheme was targeted towards all professionals within their trust. When asked if reporters could deviate from the rules of the reporting scheme, respondents (n=52) stated “Yes” 58% (n=30), “No” 13% (n=7), and “Don’t know” 29% (n=3).

Those who did not have an existing local reporting scheme were asked in their opinion how likely it was that a local scheme would be developed. The results are presented in Figure 3-2

Figure 3-2 : Likelihood of the development of a local ADR reporting scheme in secondary care NHS Trusts not currently operating an ADR scheme



3.1.8. Complaints about hospital pharmacist ADR reporting

Respondents were asked about any complaints from medical staff that they had received with regard to ADR reporting by pharmacists. Three respondents supplied examples of medical complaints they had received relating to pharmacist reporting.

These included:

Case one: A clinical pharmacist who made a clinical intervention involving an adverse drug reaction and then documented it in the medical notes and on a Yellow Card. The patient's consultant was aware of the adverse reactions, but had intentionally not intervened, as he did not wish the course of the disease to be altered. Although the pharmacist's intervention was judged to be correct by the pharmacy department, the consultant argued that the pharmacist's intervention resulted in additional tests lengthening the patient's stay in hospital. As a consequence the patient could not leave hospital and go home to die.

Case two: A difference in opinion between pharmacy staff and medical staff on whether an adverse drug reaction had occurred.

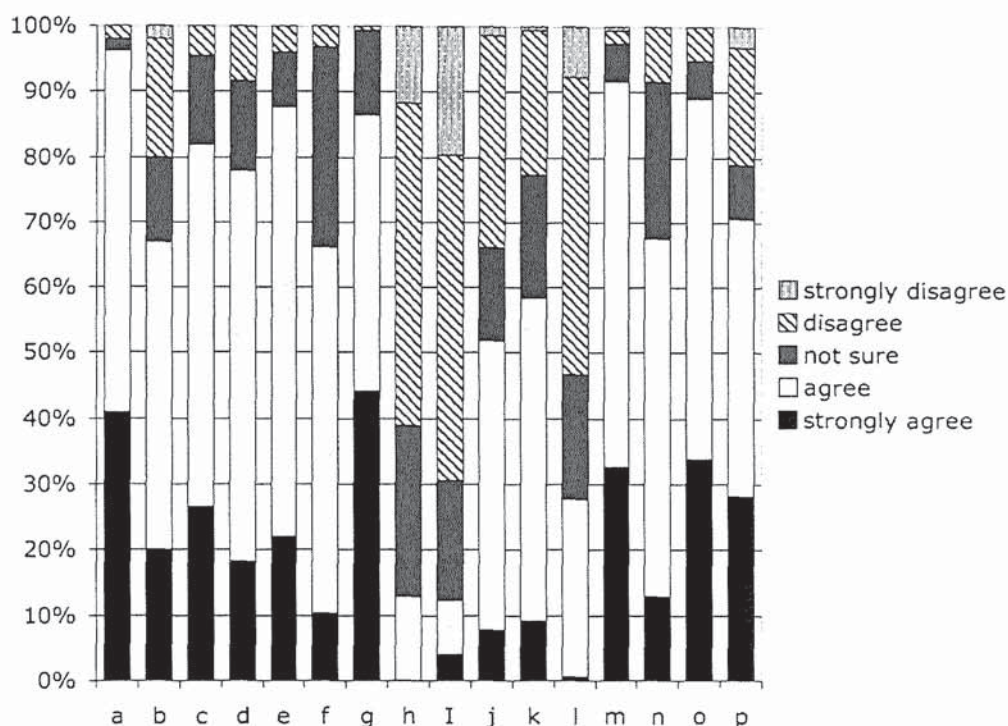
Case three: Medico-legal concerns raised by a consultant following the reporting of an adverse drug reaction.

Respondents were asked about any patient complaints that they had received with regard to pharmacist adverse drug reaction reporting. No complaints from patients were supplied.

3.1.9. Attitudes of chief pharmacists to ADR reporting

Respondents were asked to give their opinions on a number of statements by indicating their level of agreement using a five point Likert scale. All valid questionnaires (n=154) gave answers. The results are summarised in Figure 3-3 overleaf.

Figure 3-3 : Attitudes of Chief Pharmacists towards adverse drug reaction reporting



Guide to codes

a=ADR reporting is an essential component of a pharmacists role on the wards

b=Pharmacist ADR reports should be reviewed by the pharmacy department before being sent to the CSM

c=Monitoring of ADRs within my trust is a clinical governance issue

d=monitoring of ADRs should be a priority for pharmacy services

e=Pharmacists would benefit from increased training on ADR reporting.

f=Pharmacists within my trust have the competency to detect ADRs

g=Increased pharmacist time on wards in a clinical capacity would increase ADR reporting by pharmacists

h=development of a local ADR reporting scheme is no a valid use of staff performance.

i=ADR reporting is a priority of my line manager

j= ADR reporting is one of my priorities

k=ADR reporting is a priority of my clinical services pharmacist(s)

l=ADR reporting is not seen as a priority by pharmacists in my trust

m=It is a professional responsibility of pharmacists to report ADRs

n=Pharmacists have the active support of medical staff to report ADRs

o=Pharmacists have the active support of the pharmacy department to report ADRs

p=Current recruitment and retention difficulties are inhibiting pharmacist ADR reporting

Support for pharmacist reporting was widespread, 96% of respondents agreeing or strongly agreeing with the statement that *“Adverse drug reaction reporting is an essential component of the pharmacists role on the wards”*.

Surprisingly, despite this agreement, 67% of respondents stated that pharmacists Yellow Cards should be reviewed before submission to the MHRA, with only 20% disagreeing or strongly disagreeing with the statement *“Pharmacist adverse drug reaction reports should be reviewed by the pharmacy department before being sent to the CSM”*.

ADR reporting was seen by the vast majority as a clinical governance issue, with 82% of respondents agreeing with the statement *“Monitoring of adverse drug reactions within my trust is a clinical governance issue”*.

ADR reporting was also seen as a priority for pharmacy services, with 78% of respondents agreeing or strongly agreeing with the statement *“monitoring of adverse drug reactions should be a priority for pharmacy services”*.

Increased training was seen as important by a majority of respondents, with 88% agreeing or strongly agreeing with the statement: *“Pharmacists would benefit from increased training on ADR reporting”*.

While a majority felt that pharmacists had the competence to detect ADRs, 66% agreeing or strongly agreeing with the statement *“Pharmacists within my trust have the competency to detect adverse drug reactions”*, there were a significant number of respondents (30%) who were not sure about their pharmacists’ competence to detect ADRs.

A majority of respondents (86%) felt that increased time on the wards in a clinical capacity would help pharmacists report more often.

A majority of chief pharmacists disagreed with the statement that local schemes were not a valid use of pharmacy resources 60%.

There were differences in priorities reported between various groups. Twelve percent of respondents agreed or strongly agree with the statement *“Adverse drug reaction reporting is a priority of my line manager”*, while 52% of respondents agreed or strongly agreed with the statement *“Adverse drug reaction reporting is one of my priorities”*. Fifty-eight percent of respondents agreed or strongly agreed with the statement *“Adverse drug reaction reporting is a priority of my clinical services pharmacist(s)”*, and 54% disagree or strongly disagreed with the statement *“Adverse drug reaction reporting is not seen as a priority by pharmacists in my trusts”*.

Respondents from hospitals affiliated to medical schools were also statistically more likely to agree that ADRs were a personal priority (Pearson $\chi^2=13.247$, $df=2$, $P<.001$).

The majority of respondents (92%) indicated it was a professional responsibility to report adverse drug reactions.

Support from medical staff and pharmacy staff was also high with 68% agreeing or strongly agreeing with the statement *“Pharmacists have the active support of medical staff to report adverse drug reactions”*, and 89% agreeing or strongly agreeing with the statement *“Pharmacists have the have the active support of the pharmacy department to report ADRs”*.

When asked about recruitment and retention difficulties, 70% of respondents agree or strongly agreed with the statement *“Current recruitment and retention difficulties are inhibiting pharmacist adverse drug reaction reporting”*.

3.1.10. Discussion

3.1.10.1. Response rate

The high response rate (82%) to this questionnaire addressed to chief pharmacists suggests a high level of external validity. The high response rate may also be indicative of a relatively high interest in the subject of ADRs in senior hospital pharmacist management.

3.1.10.2. Discussion

Virtually all chief pharmacists noted that their hospital had a medicines management control device, such as a DTC. Chief pharmacists indicated that ADRs were a low priority for these devices, with only one in four of these devices discussing ADRs in the two years previous to the questionnaire.

Interestingly, the hospitals linked to medical schools were more likely to have discussed ADRs at the medicines management device, and were statistically more likely to have a local ADR reporting scheme being in operation. This also extended to the personal priority given to ADR reporting by chief pharmacists; those working at hospitals with links to medical schools having a statistically significant increased personal priority related to ADRs. One reason for this may be a effect from leadership from a more academic medical staff; clinical pharmacology tending to be a largely academically based discipline³²⁶. However, only four chief pharmacists noted that a specific medical member of staff was taking a particular interest in ADRs.

ADR reporting was not highly placed within the local and national benchmarking schemes that hospital at the time of the present study. In addition the present study found that the priority given to ADRs within trusts appeared low, with little support from outside of the pharmacy department, This suggested Yellow Card reporting is currently a professionally led activity with little institutional motivation to improve reporting rates. Hospital pharmacy is heavily involved in medicines management within NHS trusts, a role strengthened by the publication of the 2001 report *A Spoonful of Sugar*³²⁷. Since then the Healthcare Commission has produced annual health checks for NHS hospital trusts related to medicines management. Twenty-one medicines management indicators are included within the health check, none of which contain reference to ADR reporting via the Yellow Card scheme³²⁸. While the focus of the Healthcare Commission is with improving medicines management for the benefit of

patients within the hospitals they are assessing, consideration should be given to the inclusion of Yellow Card reporting within the indicators. It was noticeable that the present study appeared to show a decreased priority being given to ADR reporting with increasing seniority in management, with only 12% of chief pharmacists thinking ADR reporting was a priority of their line manager. A medicines management indicator that included the Yellow Card scheme could increase NHS hospital management focus on ADR reporting.

Local ADR reporting schemes were run by 37% of pharmacy departments in the present study. Local ADR reporting schemes have been in evidence long before the pharmacist reporting, with examples being found nationally in the late 1970s²¹⁴. By 1996, fifteen percent of pharmacy departments were running local ADR reporting schemes³²⁹. Following the acceptance of hospital pharmacists into the Yellow Card scheme in 1997, this rose to 19% in Green's 1999 survey of pharmacy clinical managers³³⁰. Ferguson and Dhillon²⁵⁷ found in 1998 that 35% of pharmacy departments had procedures in place for the reporting of ADRs; the difference between this and the Green's 1999 figure perhaps being due to the direction of the questionnaire to medicines information departments within pharmacy departments, rather than clinical services managers, and the use of the term procedure rather than scheme. However, Swies and Wong's 1999 survey of hospital pharmacists found that only 23% of hospital pharmacists reported that their trusts has a written policy²⁹².

However, it does appear that local ADR reporting schemes continued to develop after the introduction of hospital pharmacist ADR reporting in 1997, although plans for further schemes appear less likely than in the past. The percentage of chief pharmacists with definite plans to introduce a local scheme in the present study was 8.4%, compared to 33% in Green's 1998 survey³³⁰. This could either be due to saturation of schemes in those departments with sufficient interest in ADR reporting, or because newer priorities are being focused on such as: improved medicines management, the introduction of automated dispensing, and other

service developments such as pharmacist prescribing. A similar survey in Australia in 2001²⁹⁷, albeit with a lower response rate of 49.5%, showed a higher percentage (67%) of local ADR reporting policies in place, although no association was seen between ADR reporting and a policy being in place.

There is support for ADR reporting from chief pharmacists, who view ADR reporting as an essential part of a pharmacist's job, as well as a professional responsibility. The majority of chief pharmacists believe pharmacists have the support in this activity from the pharmacy department and medical staff within their hospital.

A number of chief pharmacists still had concerns about their pharmacists' involvement in ADR reporting. This may be due to a desire to control the quality of Yellow Cards submitted by their department, or possibly due to concerns about local medical staff complaining about such reports. However, the MHRA's judgement that pharmacist reports are of high quality, and this survey's failure to uncover any serious complaints about pharmacist ADR reporting (either from patients or medical staff), should give chief pharmacists confidence in their staff. However, nearly a third of chief pharmacists had concerns about their pharmacists' competence to detect ADRs, and a majority felt increased training would be of benefit.

The widespread view (67%) that Yellow Cards from hospital pharmacists should be screened by pharmacy departments prior to submission to regulatory authorities is of major concern. The Yellow Card scheme invites reports on the basis of a suspicion of an ADR in a patient, not on a clear-cut association. In addition, the minimum set of data that the MHRA accept (reporter details, patient identifier, suspected drug, and reaction) may be considered inadequate by the pharmacy. A potential exists that a pharmacy assessment of causality and completeness of a Yellow Card could delay submission of a valuable ADR report, or even lead to a report not being submitted. The West Midlands YCC has anecdotal experience of a local medicines information service holding onto a batch of Yellow Cards for several months

before submission. Green et al³³⁰ found in their 1998 survey that only 70% of local ADR reports were forwarded on to the Yellow Card scheme. Another initiative to detect ADRs by pharmacist monitoring of patients admitted to hospital, detected 25 suspected ADRs, yet only 2 cards were reported³³¹. An early local ADR reporting scheme describes how after examining 79 suspected ADRs, 35 were not submitted to the Yellow Card scheme after *“it was considered that the patient’s drug history did not coincide with the onset conclusion of the reaction, or the documentation and clinical history were inadequate to incriminate the suspected drug”*²¹⁶.

To this extent, if local ADR reporting schemes act as a barrier to Yellow Cards reaching the MHRA, then they are counterproductive. Local reporting schemes should be focused on the promotion of participation in the Yellow Card scheme, rather than acting as quality control for ADR reports. Local schemes that have taken on that role have continued to be valuable in promoting the use of the Yellow Card scheme^{256,332} even after the introduction of hospital pharmacist ADR reporting. The presence of a local procedure, promotion of ADR reporting, education and designated ADR staff has been associated with higher, admittedly self-reported, levels of ADR reporting²⁵⁷.

If part of the desire to collate ADR reports locally via schemes is to obtain a measure of the hospital reporting rate, then that would give further weight to the argument that the MHRA should provide reports of the number of Yellow Cards generated by NHS trusts as feedback.

Recruitment difficulties, and time available for pharmacists’ clinical activity, are also seen as important by chief pharmacists. The majority of pharmacists’ time when spent on the ward is prioritised on clinical activities³³³, and there is evidence that increased workload can have a detrimental effect on the pharmacists monitoring of appropriate prescribing³³⁴. Recruitment difficulties that place strain on hospital pharmacy departments would therefore reduce pharmacists’ clinical activity – reducing their ability to detect ADRs and time available to

report them. Lack of time has been noted as a factor influencing reporting in other studies²⁹⁰⁻²⁹². In 2001, the year before this study, recruitment difficulties in hospital pharmacy were apparent with 3,929 full-time equivalent jobs available. In 2007, the number of jobs has increased to 6,062 full-time equivalent posts³³⁵. Although some recruitment problems continue, it is to be hoped that the increased hospital pharmacist workforce and movement into expanded clinical roles will improve Yellow Card reporting performance.

3.1.11. Conclusion

The present study found that chief pharmacists strongly supported Yellow Card reporting by hospital pharmacists. However, there were significant concerns about the training of their staff and their competence to detect ADRs. Training is seen as important. In addition, a sizable minority of chief pharmacists believe that hospital pharmacists' Yellow Cards should be screened by pharmacy departments, possibly due to concerns about the quality of reports or potential conflict with medical staff. However, the lack of complaints concerning ADR reporting by pharmacists found in this study and the published evidence from the MHRA should lower these concerns.

Local schemes continued to be important within hospital pharmacies, although there appeared to be a reduction in the number of pharmacy departments planning new ADR reporting schemes. Such schemes should concentrate on the promotion of ADR reporting, rather than acting as a quality control screening ADR reports.

Drug and Therapeutics Committees currently give a low priority to ADR reporting, as do line managers of chief pharmacists. The MHRA should consider approaching the Healthcare Commission with a view to creating a medicines management criteria concerned with Yellow Card reporting, which would then act as an institutional driver for improving the priority given to ADR reporting with acute NHS hospital trusts.

Chapter 4 Medical and pharmacy undergraduate education in ADR reporting

Concern about the extent of training with regard to adverse drug reaction reporting has been expressed in a recent British Medical Association report on Yellow Card reporting¹⁶¹. Education has also been cited as a key factor in influencing the decision of health professionals to report²⁹², and in addition concern has been expressed about the extent of clinical pharmacology training in undergraduate medical training³³⁶. Little is known about the extent of teaching about the Yellow Card scheme within UK schools of pharmacy.

Consequently, the aim of this part of the study was to determine the extent of teaching about the Yellow Card scheme and ADRs within UK schools of medicine and pharmacy.

The objectives of this part of the study were to;

- Measure the extent of teaching about adverse drug reactions in UK pharmacy and medical schools.
- Determine the nature and number of individuals providing teaching on adverse drug reactions and the Yellow Card scheme.
- Determine the extent to which the Yellow Card scheme was present in Medical and Pharmacy course assessments.
- Determine the views of heads of pharmacy and medical schools on the provision of educational materials about the Yellow Card scheme to students.

The results were obtained from the self-completion questionnaire “Survey of undergraduate education concerning the adverse drug reactions” which was mailed to heads of schools of pharmacy and schools of medicine. A copy of the questionnaire is included in Appendix IV.

4.1. Results

4.1.1. Response rate

Three successive mailings were sent to the 16 heads of pharmacy schools and 29 heads of schools of medicine. The number of questionnaires returned for each mailing is summarised in Table 4-1.

Table 4-1: The cumulative and final proportions of questionnaires returned by respondents after successive mailings.

Questionnaire mailing	Number of questionnaires returned	Cumulative total of questionnaires returned	Returned questionnaires as proportion of total sent (%)
Pharmacy School			
1st	10	10	62.5
2nd	2	12	75
3rd	2	14	87
Medical School			
1st	16	16	62
2nd	4	20	77
3rd	2	22	85

Overall, for both medical and pharmacy schools, of the 45 questionnaires mailed, 80% (n=36) were returned and one of these was not completed (an overall response rate of 78%).

4.1.2. Reason for non-completion

One questionnaire was returned from a medical school uncompleted, citing the reason for its return as “lack of time”. It is not known why others were not returned.

4.1.3. Nature of respondents

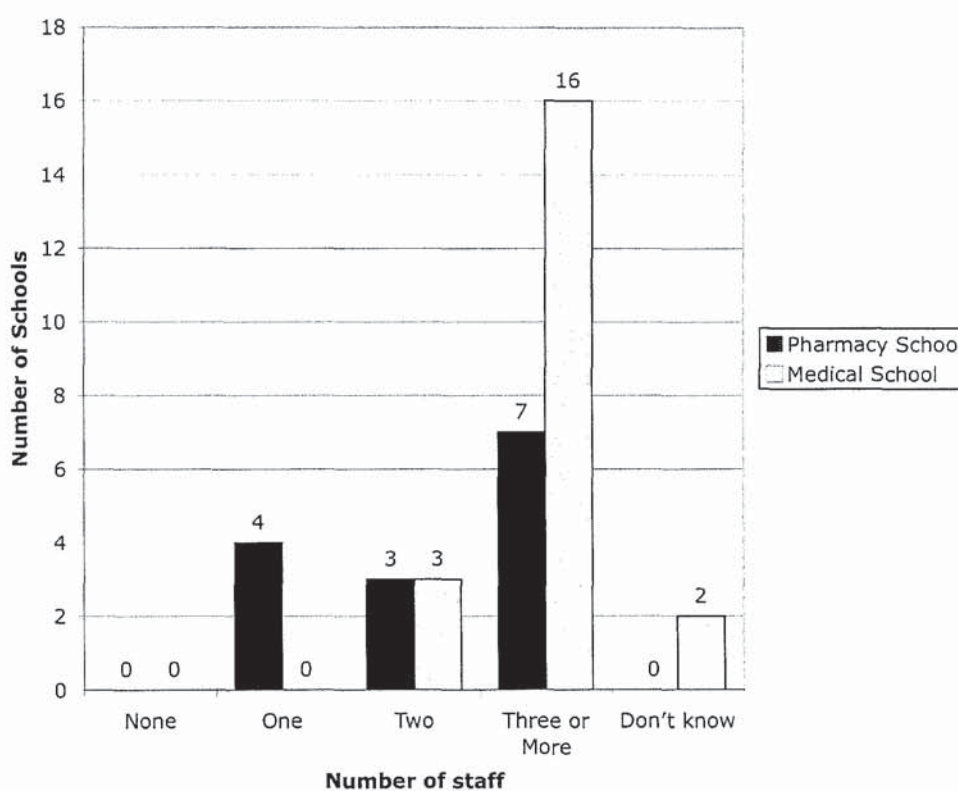
Although the questionnaire and covering letter was addressed to individual heads of schools, it was clear that one questionnaire had been directed towards another individual within the school. Who was ultimately responsible for completion of the questionnaire was beyond the

control of the investigator, however it is likely that in some cases questionnaires may have been passed on to academic staff who were considered by the head of school to be in the best position to answer the questionnaire.

4.1.4. Staff involved in teaching

Respondents were asked how many individuals were responsible for teaching students about adverse drug reactions. These results are depicted in Figure 4-1.

Figure 4-1: Number of staff responsible for teaching students about adverse drug reactions within pharmacy and medical schools



More than three members of staff were involved in the teaching of ADRs at 76% of medical schools, whereas only 50% of pharmacy schools had similar levels of staff involvement. In all medical schools more than one individual was involved in ADR teaching, whereas 29% of pharmacy courses reported the involvement of a single individual.

Respondents were asked about the subject specialisations of the individuals responsible for teaching students about ADRs. In pharmacy programmes, pharmacy practice was the most frequently cited specialisation (n=10) of academic staff involved in teaching about ADRs. In medicine, clinical pharmacology and therapeutics (n=14) was the most common specialisation associated with ADR teaching. The full range of specialities associated with adverse drug reaction reporting are summarised in Table 4-2.

Table 4-2: Specialisations of academic staff involved in teaching about ADRs in UK Pharmacy and Medical schools

Pharmacy Schools (25)	Medical Schools (32)
Pharmacy Practice (10)	Clinical pharmacology (14)
Pharmacology (6)	Pharmacology (6)
Toxicology (4)	Toxicology (4)
Clinical Pharmacy (4)	Pharmacy (3)
Natural Products (1)	All medical specialisations (1)
	General medicine (1)
	Primary care (1)
	Internal medicine (1)
	Medical Defence Union (1)

4.1.5. Place of the Yellow Card scheme in curriculum and assessments

Respondents were asked about the inclusion of the Yellow Card scheme within the undergraduate programme. The vast majority of respondents stated that the Yellow Card scheme featured in the undergraduate syllabus. The results are shown in Table 4-3.

Table 4-3 : The place of the Yellow Card scheme in Pharmacy and Medical undergraduate syllabus

Detail	Course	Yes	No	Don't Know
		Number of Responses		
Yellow Card scheme included in Syllabus	Pharmacy (n=14)	11	2	1
	Medicine (n=21)	18	1	2

A Chi-squared test showed no statistically significant difference between Pharmacy and Medical School (Pearson $\chi^2=0.996$, df=2, P=0.608).

Respondents were asked about the inclusion of the Yellow Card scheme within the undergraduate programme assessment. Course assessments contained questions about the Yellow Card scheme in 79% of pharmacy programmes and 57% of medical programmes. The full results are summarized in Table 4-4.

Table 4-4 : Use of the Yellow Card scheme within course assessments

		Yes	No	Don't Know
Detail	Course	Number of Responses		
Yellow Card Scheme included in course assessments	Pharmacy (n=14)	11	3	
	Medicine (n=21)	12	7	2

A Chi-squared test showed no significant difference between the use of Yellow Card assessments in pharmacy schools and medical schools (Pearson $\chi^2=2.337$, df=2, P=0.311).

Respondents were asked about the use of non-university specialised speakers who taught practical aspects of the Yellow Card scheme. Specialist speakers from external bodies were used by only a minority of both pharmacy and medical schools. The data is summarized in Table 4-5

Table 4-5: The use of specialist staff in teaching programmes

		Yes	No	Don't Know
Detail	Course	Number of Responses		
Use of specialist staff to lecture on practical aspects of the Yellow Card scheme.	Pharmacy (n=14)	3	11	
	Medicine (n=21)	5	15	1

Half those courses that invited external speakers involved expert speakers from the MHRA, the remainder inviting speakers from the NHS or the Medical Defence Union. There was no indication of the grade or seniority of the speaker. The list of speakers is noted in Table 4-6.

Table 4-6: Source of external speakers on the Yellow Card scheme

Pharmacy Schools	Medical Schools
Medicines Information	MHRA (3)
Regional Monitoring Centre	Medical Defense Union
National Health Service	National Health Service

4.2. *Provision of material to students*

Fewer than half of respondents provided students with a guide to reporting ADRs (43% pharmacy schools and 43% medical schools). The remainder agreed that such a guide might be useful, with the exception of one respondent from a medical school and one respondent from a pharmacy school who were unsure if such a guide would be useful and two (10%) from medical schools who did not think such guides would be useful. These results are presented in Table 4-7.

Table 4-7 : Views on the provision of a guide to Yellow Card reporting

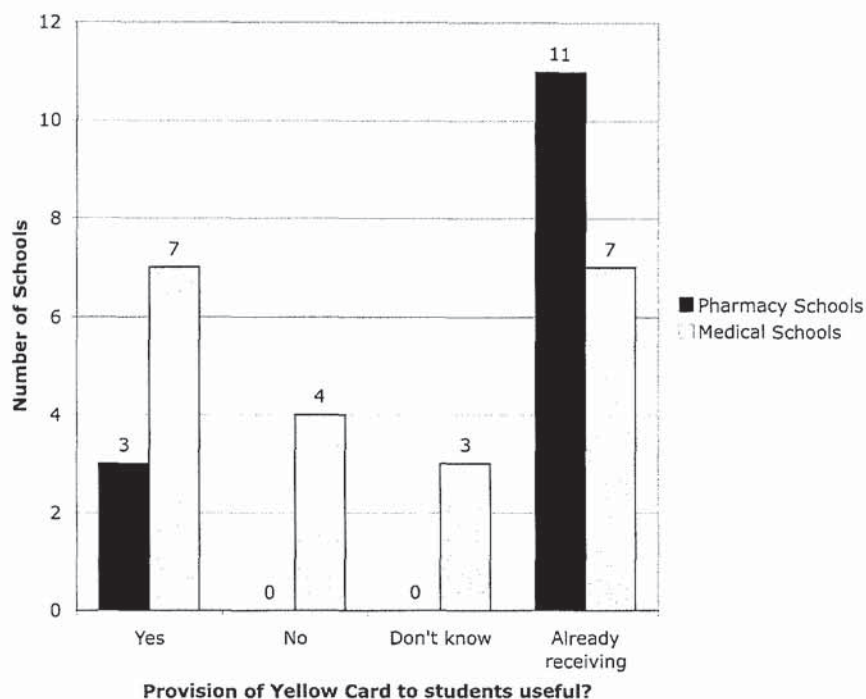
		Useful	Not useful	Don't know	Already receiving
A practical guide to reporting to the Yellow Card Scheme	Pharmacy (n=14)	7	0	1	6
	Medicine (n=21)	9	2	1	9

A Chi-squared test showed no significant difference between responses from pharmacy and medical Schools (Pearson $\chi^2=1.510$, df=3, P=0.680).

Seventy-nine percent of pharmacy schools reported that students were supplied with a Yellow Card, in contrast to only 33% of medical schools. One in five heads of medical

schools thought that the provision of a yellow card would not be helpful to students in their training. These results are depicted in Figure 4-2.

Figure 4-2: Provision of Yellow Card to students

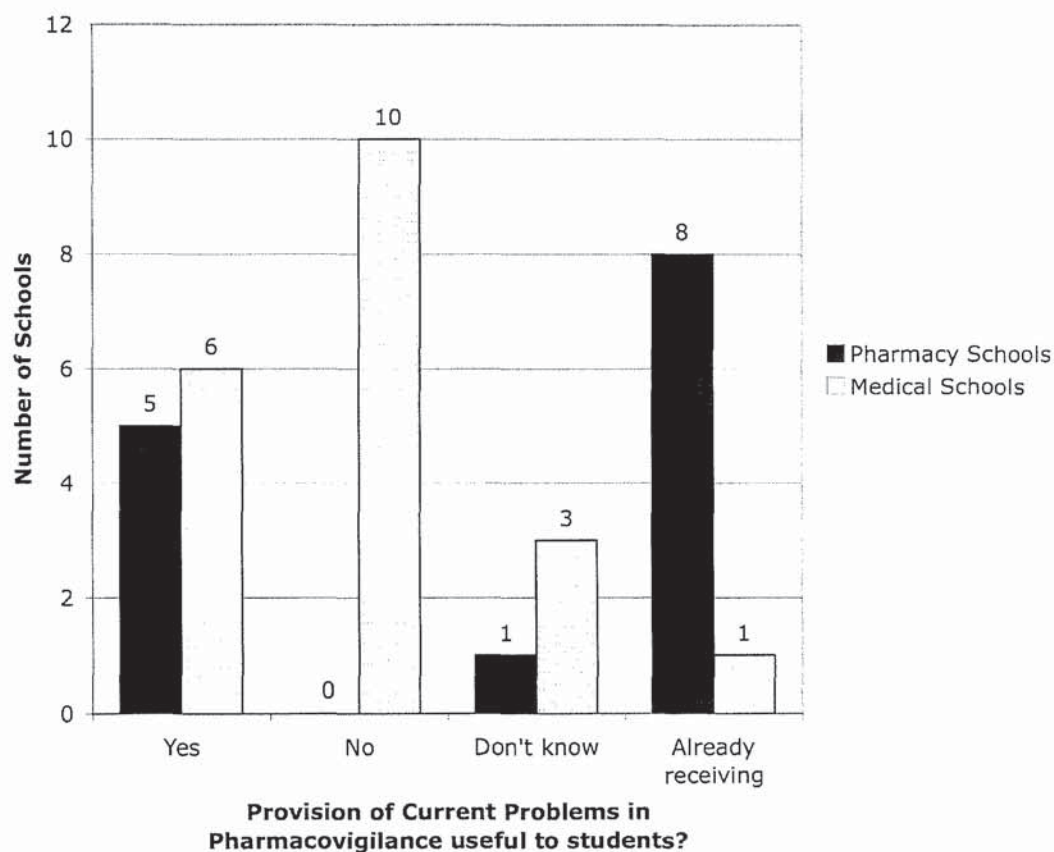


A Chi-squared test showed a significant difference between the results from pharmacy and medical schools (Pearson $\chi^2=8.426$, $df=3$, $P=0.038$). However, as 62.5% of cells had an expected count of less than 5 this result may be misleading. As there was no valid way to reduce the collapse the responses to two, a Fisher's exact test could not be performed.

The CSM's publication "*Current Problems in Pharmacovigilance*" was made available to undergraduates in 57% of pharmacy schools, but in only 5% of medical schools. Of those schools not already providing "*Current Problems in Pharmacovigilance*" 35% of pharmacy school and 30% of medical school respondents indicated that such provision would be helpful. Fifty per cent of medical school respondents felt that the provision of "*Current*

Problems in Pharmacovigilance“ would not be helpful to students. These results are in Figure 4-3.

Figure 4-3: Views on the provision of Current Problems in Pharmacovigilance to pharmacy and medical students



A Chi-squared test showed a significant difference between responses from pharmacy and medical schools (Pearson $\chi^2=15.974$, $df=3$, $P=0.01$). However as 62.5% of cells had an expected count of less than 5 this result may be misleading. As there was no valid way to reduce the collapse the responses to two, a Fisher’s exact test could not be performed.

4.3. Discussion

4.3.1. Response rate

The overall response rate to the survey was high at 78%, suggesting that the results may be representative of the situation at the time survey was undertaken.

4.3.2. Teaching and assessment of ADRs within medical schools

The present study demonstrates that teaching about ADRs in medical schools was generally allocated to staff with a traditional specialisation such as clinical pharmacology, pharmacology or toxicology. Although, the Yellow Card scheme was within the syllabus of the majority of surveyed medical schools (86%), inclusion of the Yellow Card scheme within course assessments was lower (57%).

The prominence of clinical pharmacology and therapeutics (CPT) as the main source of education about the Yellow Card scheme within medical courses is not unsurprising. CPT is the natural home of drug safety issues, and post-marketing surveillance. For example, all the current heads of regional Yellow Card Centres are clinical pharmacologists. For that reason, the teaching of pharmacovigilance is tied to the leadership provided by CPT within medical schools.

CPT came to prominence in the 1960s, in the wake of concerns about drug safety and the prominence of strong research groups in clinical medicine³³⁷. In 1970, Professor O.L.Wade, a member of the original Committee on the Safety of Drugs, wrote¹⁵:

“Medical schools in Britain, with a few exceptions on the Celtic fringe, have recently neglected clinical pharmacology. [...] The establishment of full-time chairs in these subjects is an urgent need in any medical schools where they do not already exist. Undergraduate students need instruction on the proper use of drugs, knowledge of their common adverse reactions and appreciation of the dangers of their misuse.”.

Such concerns have now become contemporary. CPT in the UK is in a process of decline, with only 68 specialists remaining in the UK in 2003, with almost half of those due to retire in the next ten years. In contrast to an increase in medical specialists from 1993 to 2003 of

79%, CPT specialists declined by 24%³²⁶. A survey of academic clinical pharmacologists performed in 1996, noted recruitment difficulties and noted that careers were more likely to be found in the industry, rather than into academic medicine³³⁷. Concerns about the decline of CPT is not confined to the UK³³⁸.

Although, part of the loss of CPT specialists may be due to high profile CPT specialists being recruited into senior positions within national organisations concerned with drug regulation, drug safety, and technology appraisal, Maxwell and Webb³²⁶ argue that other factors have worsened the decline of CPT:

Performance is difficult to measure in CPT, putting it at a disadvantage in a target driven NHS.

CPT's involvement with cardiovascular management has declined as primary care and cardiology has taken over that field.

CPT's largely academic base has been undermined by changes in medical education, leading away from a collection of disciplines towards an integrated problem-based approach.

This last change was arguably driven by publication of *Tomorrow's Doctors*³³⁹ by the General Medical Council in 1993. *Tomorrow's doctors* argued that teaching individual compartmentalised scientific areas was disadvantageous in comparison to a more integrated medical curriculum. It emphasised system-based learning and the eradication of a preclinical/clinical divide, with a seamless integration of education and practice as a doctor³⁴⁰. It was argued that this process had the unfortunate side effect of the loss of dedicated CPT courses and assessments³⁴¹, which had previously been a common feature of medical undergraduate courses. Teaching about CPT issues, such as safe prescribing and pharmacovigilance, became scattered, or lost, throughout the integrated curricula. Established departments of clinical pharmacology were closed, or underwent mergers as part of rationalisation exercises in response to external research assessments. This reduction in CPT lead to decreased opportunities to educate undergraduates about CPT issues, such as safe

prescribing and pharmacovigilance, although others have argued that deficiencies in medical prescribing are more deep-rooted³⁴². Concerns have also been expressed by both medical students and teachers about the teaching of clinical therapeutics within the UK³⁴³⁻³⁴⁶.

Such concerns are not limited to the UK. A US survey of undergraduate and graduate medical education was performed in 2000^{347,348}. Fifty-three percent of schools did not have clinical rotations that included clinical pharmacology or ADR training. In those that did provide such training, it was only mandatory in a minority of courses (8%), with the rest providing an elective option for such training. There was widespread support among course directors for heightened awareness of training in ADRs.

Much of the concern about the decline of CPT has been expressed in terms of the potential effects on safety of prescribing by doctors given the increasing complexity of modern therapeutics^{336,349}, and the need for all doctors to have a firm grounding in the principles of therapeutics, such as; the risk and benefits of prescribing medication, evidence-based prescribing and the monitoring of drug safety.

The National Audit Office report “Spoonful of Sugar”³²⁷ stated that:

Concerns have recently been expressed that the core curricula at medical schools do not provide a thorough knowledge of safe medicines prescribing and administration. Shortcomings in doctors' knowledge means that there is a particular risk of medication errors when they first arrive in hospital. Only a small proportion of new doctors believe that their induction dealt adequately with medicines management issues

After a review of the effects of the 1993 *Tomorrow's Doctors*, a revised version was issued to replace the 1993 guidance. Specific references to the effective and safe use of medicines, including adverse effects and drug interactions, were inserted. The current version of *Tomorrow's Doctors*³⁵⁰, published in 2002, notes that:

The Graduates must know about and understand the principles of treatment including the following [...]

effective and safe use of medicines as a basis for prescribing, including side effects, harmful interactions, antibiotic resistance and genetic indicators of the appropriateness of drugs.[...]

And Graduates must be able to do the following safely and effectively [..]

e.g. Work out drug dosage and record the outcome accurately.

Write safe prescriptions for different types of drugs.

Critics of the 1993 Tomorrow's Doctors did acknowledge that the 2002 version was a turning point, in particular welcoming the increased focus effective assessment of students competency and the implicit GMC recommendation that all UK graduates should be safe prescribers. In 2003, the British Pharmacological Society (BPS) issued a core curriculum for teaching safe and effective prescribing, which made explicit mention of the importance the Yellow Card scheme³⁵¹. The present study does point out that a number of medical schools (43%) are still not placing Yellow Cards within course assessments. It is not known if the BPS guidance has been widely taken up by medical schools.

Whiting et al³⁵² put forward four guidelines and a series of key questions that should be asked in problem-based-learning exercises related to the safe and effective use of drugs, in order to help mitigate the apparent reduction in the formal teaching of CPT. Questions that students were asked to consider with regard to safe prescribing included some concerned with adverse reactions, such as *"What are the potential side effects?"* Based upon the findings from the present study, it is suggested that an additional question that should be asked in problem-based-learning exercises when an adverse drug reaction is present: *"Should this adverse drug reaction be reported to the regulatory authorities?"*

Despite these advances in improving the teaching of CPT difficulties continue. A symposium at the BPS in December of 2005³⁴⁰, noted that too few clinical pharmacologists existed in order to give a lead to all medical schools in the UK, and suggested that centralised e-learning could be developed at a national level which could be used within schools. It was

suggested that key stakeholders involved in this process could be the Department of Health, the National Prescribing Centre and the BPS. An approach of this nature has been described by the Australian National Prescribing Service, where such a series of interaction modules have been taken up by a majority of Australian medical schools³⁴⁶.

Yellow Card Centres have something to offer in this regard. Already staffed with clinical pharmacologists, and support staff such as pharmacists, they could provide materials for undergraduate training. Indeed, Yellow Card Centres are already providing undergraduate education to some universities.

Concern about the safe use of medicines by medical staff has led to attempts to improve training in the areas of safe prescribing and drug administration^{344,353,354}, and in the more general areas of clinical therapeutics. Langford et al³⁵⁵ tested practical aspects of therapeutics of medical students by use of an objective structured clinical examination (OSCE). The examination of knowledge about adverse drug reactions and Yellow Card reporting was specifically mentioned as an area assessed in their OSCEs.

Durrieu et al³⁵⁶ in a study of French medical students has demonstrated that the provision of a pharmacology course markedly increased the awareness of French medical students towards adverse reactions. Students were asked to rank the perceived risk of several classes of drugs on a visual analogue scale prior to training and post training. When all classes of drugs were taken as a whole median scores of the perceived risk rose from 4.8 (± 1.3) before the course to 5.8 (± 1.5) after the provision of pharmacological training. ($p < 0.0001$). While the study was conducted the withdrawal of rofecoxib occurred, leading to possible exposure of students to media publicity about the risks of medicines. However, the authors suggest that pharmacology training raises awareness of the potential for serious harm from drugs. The figure prior to training was lower than figures obtained by Bongard et al¹⁹⁴ when they comparing various groups of professionals to the general public using the same analogue

scale. After training, the students were in second place after pharmacists, and before pharmacovigilance professionals in third place, for the global perception of risk.

4.3.3. Teaching and assessment of ADRs within pharmacy schools

The present study demonstrates that teaching about ADRs was performed in a majority of schools by either pharmacy practice or pharmacology, as well as in four schools by clinical pharmacy. There is a concern about terminology used by respondents; terms such as pharmacy practice and clinical pharmacy may be interchangeable by heads of schools of pharmacy. It is arguable that pharmacy practice and clinical pharmacy are the pharmacy equivalent of CPT taught in medical schools, being concerned with the practical application of pharmacological knowledge to real-life practice.

The Yellow Card scheme was within the syllabus of the majority of surveyed medical schools (79%), with all those schools using the Yellow Card scheme in assessments. However, there was no statistically significant difference between the use of the Yellow Card scheme in assessments between medical and pharmacy schools.

The UK MPharm degrees are accredited by The Royal Pharmaceutical Society of Great Britain (RPSGB), who provide an indicative syllabus on which UK degrees base their content³⁵⁷. The indicative syllabus currently contains the item: *“Clinical evaluation of new and existing drugs and medicines, and post-marketing surveillance. Good clinical practice.”* The present study would indicate that the majority of UK pharmacy courses do include teaching and assessment of the Yellow Card scheme, which is a cornerstone of the post-marketing surveillance, however there are a number of schools which do not.

Currently, the RPSGB is undertaking a root and branch review of educational policy which will take place over the next two to three years³⁵⁸. One of the key aspects will be what is to be taught, learned and assessed. Although, current pharmacy courses do appear to be teaching students about the Yellow Card scheme, the consultation does give an opportunity to ensure

that pharmacovigilance issues, and specifically the Yellow Card scheme, are given due prominence with undergraduate education.

Undergraduate pharmacy courses have recently lengthened from three years to four years, partly in order to augment the therapeutic knowledge of students. Changes in the teaching of therapeutics are being seen in pharmacy courses, and an emphasis on the practical application of skills and clinical knowledge is becoming more common³⁵⁹. Concern about reduced formal teaching of therapeutics in pharmacy courses has not been expressed.

The MHRA originally intended that community pharmacists would be a valuable source of Yellow Card reports of ADRs from complementary medicines, however this has been of limited success. It is therefore notable that one school of pharmacy included ADRs in the 'natural product' subject area. Given the increasing use of complementary medicines, and their potential to cause ADRs, it is desirable that the importance of Yellow Reporting to alternative therapies such as herbs is included in any teaching about the Yellow Card scheme. Sears and Generali³⁶⁰ conducted a survey of pharmacy students' knowledge of the reporting of ADRs and medication in the US in nine colleges of pharmacy. The survey elicited poor response rates (from 8% to 38% depending on the year of the student), and only 9 out of 88 potential schools of pharmacy participated. However, it did show that while awareness of the FDA Medwatch scheme was high in students in later years of pharmacy courses, there was less knowledge about the location of reporting cards and the process of reporting.

4.3.4. The use of external speakers to teach about ADRs

There was a low level of use of external specialist speakers in both pharmacy and medical schools. Only 3 pharmacy schools and 6 medical schools invited external speakers from outside organisations, and only in four cases was this related to the MHRA directly, or a Yellow Card centre. There is therefore considerable opportunity for the MHRA, and its Yellow Card centres, to investigate if they can provide increased educational input into

undergraduate medical and pharmacy education. The MHRA could co-ordinate the provision of expert speakers on the Yellow Card scheme to undergraduate programmes.

Opportunity does exist for regulatory authorities to make a bigger contribution to undergraduate programmes, by providing teaching materials.

4.3.5. The presence of Yellow Cards in student assessments

Assessment is an essential component of problem-based learning; however there appears to be no assessment of reporting to the Yellow Card scheme in 43% of medical schools and 21% of pharmacy programmes. This deficiency should be addressed at an individual school level in both medical schools and pharmacy schools.

4.3.6. The provision of material related to ADRs to students

The majority of both pharmacy and medical schools, who did not already provide a practical guide to reporting to the Yellow Card scheme, reported that such a guide would be useful. The supply of an information pack targeted at undergraduate health professionals might be a useful contribution to improving awareness of the MHRA and the Yellow Card Scheme.

Some respondents from medical schools expressed reservations about how helpful material related to the Yellow Card scheme might be to students. For example, although many medical and pharmacy schools make "*Current problems in Pharmacovigilance*" available to students, nearly half of medical schools felt that supplying to students would not be useful. It is not clear from the present study why this is so, although concern about overloading students on an already intensive educational programme is one possible reason.

4.3.7. Study limitations and respondents

Although this survey had an overall response rate of 78% it has some limitations. In order to elicit a high response rate it was necessarily a short survey, which could only provide a very limited look at the teaching about ADRs and the Yellow Card scheme. The present study did not examine the quantity of the ADR teaching, the delivery methods or the method of

assessment – which are all of importance in establishing ADR reporting as important in the minds of undergraduates.

Since this study was undertaken, there has been an expansion in the provision of medical (from 29 to 31) and pharmacy schools (from 16 to 23). It is not known what the provision of information about the Yellow Card scheme is within these new schools.

4.4. Conclusions

A high proportion of both medical and pharmacy schools currently include details of the Yellow Card scheme in their syllabuses. As pharmacists have only been recognised reporters in the UK since 1997, it is encouraging that pharmacy courses appear generally to have incorporated the Yellow Card scheme in the undergraduate programme. It is not known to what extent this was the case before 1997.

However, the variation in the specialisations of those teaching about ADRs, the variability of the supply of educational materials and the low use of expert external speakers, show some areas in which the MHRA could increase their involvement in undergraduate education in order to support future reporting rates to the Yellow Card scheme.

Since the present study was conducted a National Audit Office (NAO) Report “*Safety, quality, efficacy: regulating medicines in the UK*” has been published concerned with the performance of the MCA¹⁶⁶. Part of NAO report argued for better links between the MHRA and health professionals. They stated “*whilst medical students receive technical tuition on the potential for adverse reactions and interactions with medicines, their undergraduate education does not cover the arrangements in place for licensing and monitoring medicines or a discussion of the role of the agency.*” The NAO called for the role of the MHRA and the reporting of ADRs to be fully integrated into both undergraduate and postgraduate syllabuses. A similar call has come from the House of Commons Committee of Public

Accounts¹⁶⁷, who recommended that the MHRA should increase the awareness of the Yellow Card Scheme by working with Royal Colleges and universities to develop training on medicines safety monitoring. Given the high profile the safety of medicines receives in the media, such political pressure and scrutiny is likely to continue. Although the present study is quite limited in its nature, it does suggest there is a need to improve teaching and assessment of student knowledge of the Yellow Card scheme, and also that there are opportunities for the MHRA to develop materials for use within undergraduate courses.

More recently, anger has been expressed about the withdrawal of government funding to provide medical students with the British Medical Formulary³⁶¹. Currently the BNF is a useful source of information about the Yellow Card scheme, and prominently advertises the Yellow Card scheme on its cover. The Yellow Cards contained within it are highly visible. Less student contact with the BNF may lead to less exposure to the Yellow Card scheme.

Both pharmacy and medical courses are currently undergoing significant change in terms of both structure and curriculum, and expansion in the number of courses. However, despite widespread concerns about the formal teaching of CPT in medical schools, it does appear that the Yellow Card scheme is highlighted to students. However, further declines in CPT teaching in medical schools, could put at risk the opportunity to instil knowledge and values that support the Yellow Card scheme into future professional behaviour. Pressure from CPT advocates appears to have led to some acknowledgement of the importance of ensuring that medical students are exposed to the Yellow Card scheme.

More positively, the results of this survey show that the majority of medical schools do include the Yellow Card Scheme in the syllabus, despite the concerns about the teaching of CPT. It is important to note that the present study did not seek to determine if any teaching about ADRs was mandatory, and nor did it attempt to quantify the amount of teaching dedicated to the subject of ADRs and the Yellow Card scheme.

Chapter 5 Retrospective analysis of ADR reporting in the West Midlands

In recent years concern has been expressed about levels of reporting of ADRs via the Yellow Card scheme. This concern has been expressed by the House of Commons Committee of Public Accounts in 2003¹⁶⁷, a House of Commons Health Committee in 2005¹⁰⁹, the MHRA commissioned “*Independent review of Yellow Cards*” in 2004¹⁵⁶, a National Audit Office report “*Safety, quality, efficacy: regulating medicines in the UK*” in 2003, and by the BMA¹⁶¹.

In recent years a number of changes have been made to the Yellow Card scheme, such as the broadening of the reporting base and the extension of the scheme to patients in 2005. At the same time the NHS has undergone a series of reforms, as well as major contractual changes for general practitioners – including increased use of financial incentive systems for the provision of clinical care.

The aim of the present study was to evaluate and describe the reporting demographics of spontaneous reports submitted to the West Midlands Centre for Adverse Drug Reactions in relation to national reporting data, and in relation to a number of potential indicators of performance.

The objectives of this part of the study were to;

- Identify any long-term trends in the reporting of adverse drug reactions in the West Midlands.
- Compare West Midlands region reporting with other national data related to ADRs.
- Report on the demographics of adverse drug reaction reporting within West Midlands PCTs and determine the influence of various characteristics of PCTs upon adverse drug reaction reporting rates.
- Report on the demographics of adverse drug reaction reporting with West Midlands Acute NHS Trusts and any possible relationships between reporting rates and NHS indicators of quality (Medicines Management Indicators).

The information sources used are fully described in Chapter 2, as are the methods and statistical analyses undertaken within this chapter.

5.1. Reporting trends in the West Midlands region 1994 to 2005.

The mean number of ADR reports per year since full year counts were kept by the West Midlands Centre for Adverse Drug Reactions was 1178 (range 926 to 1318) between 1994 and 2005. Data was also obtained from West Midlands YCC Annual reports. Trends in reporting are in Figure 5-1. During 2000, there was a mass campaign of meningitis C vaccination. Nurses and general practitioners were asked to report any suspected reactions, no matter how trivial, to meningitis C vaccine. Additionally, in 2000, the anti-smoking drug bupropion was launched. This led to a large influx of reports, which resulted in large changes in the level of ADR reporting. Figure 5-1 shows reporting levels of adverse reactions, both with and without meningitis C vaccine reports for the years 1999, 2000, and 2001.

Figure 5-1 : Spontaneous adverse drug reactions received by the West Midlands Centre for Adverse Drugs Reactions between 1994 and 2005

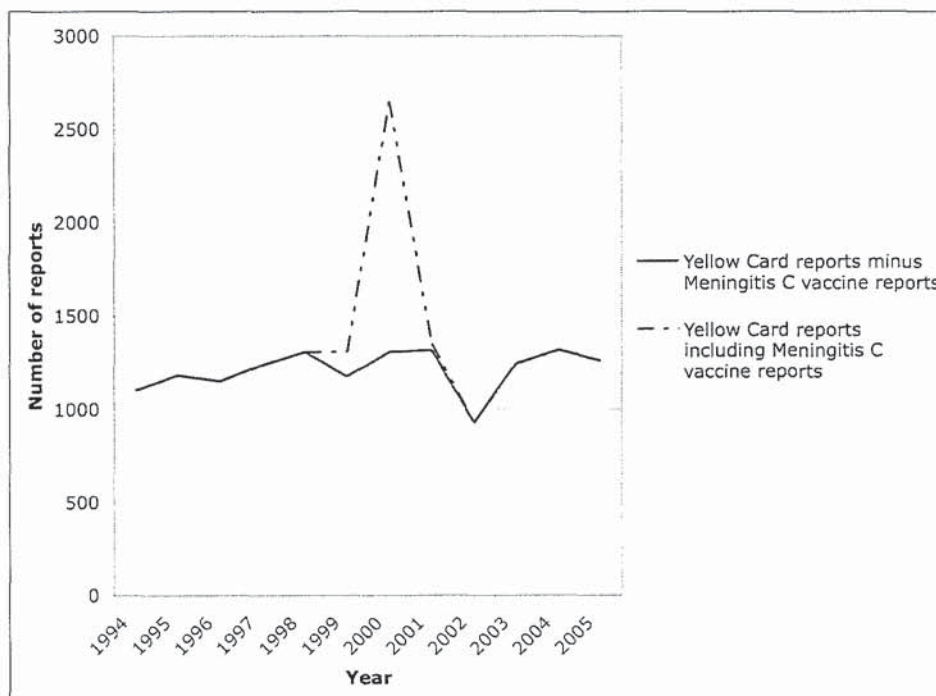
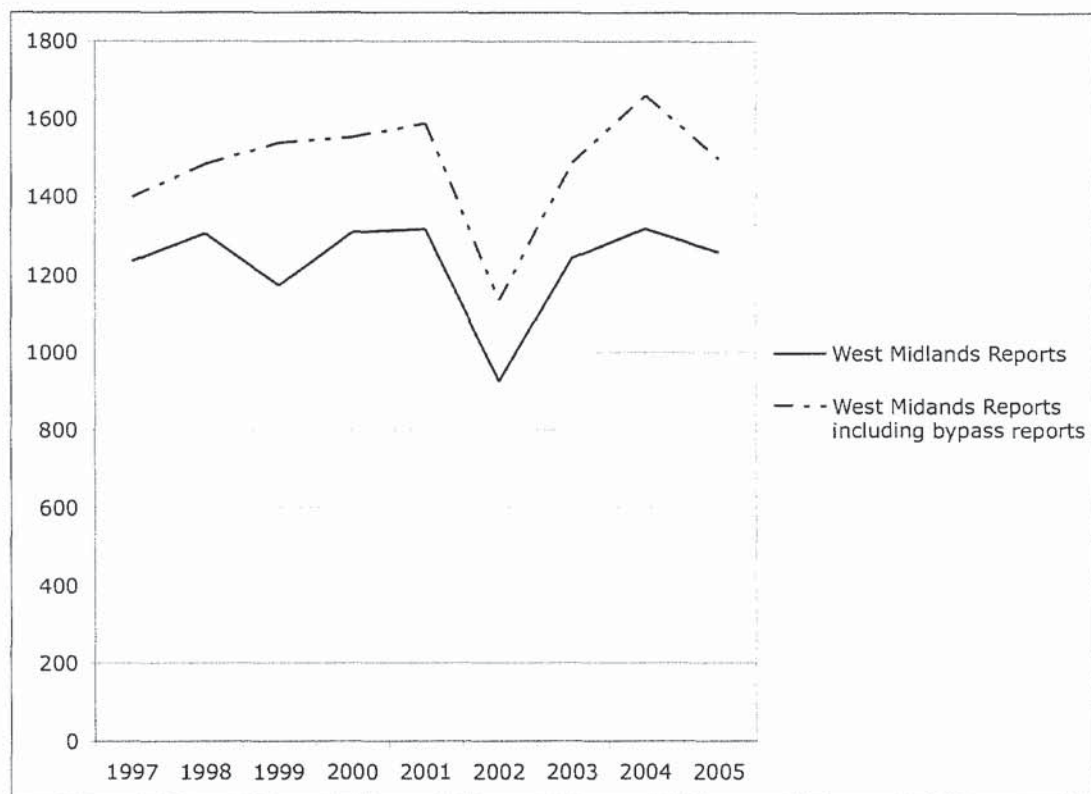


Figure 5-1 does not include all ADR reports made in the West Midlands, since a number of reports made by West Midlands reporters are sent directly to the MHRA based in London. ADR reports originating in the West Midlands that were sent directly to London are termed bypass reports. Bypass report data for the West Midlands was available from 1997 to 2005. The bypass data added an average of 19% of reports per year (Range 13.2% to 26%). The addition of bypass data did not change underlying trends in reporting (Figure 5-2). Meningitis C vaccine reports from 1999 to 2001 are excluded from Figure 5-2.

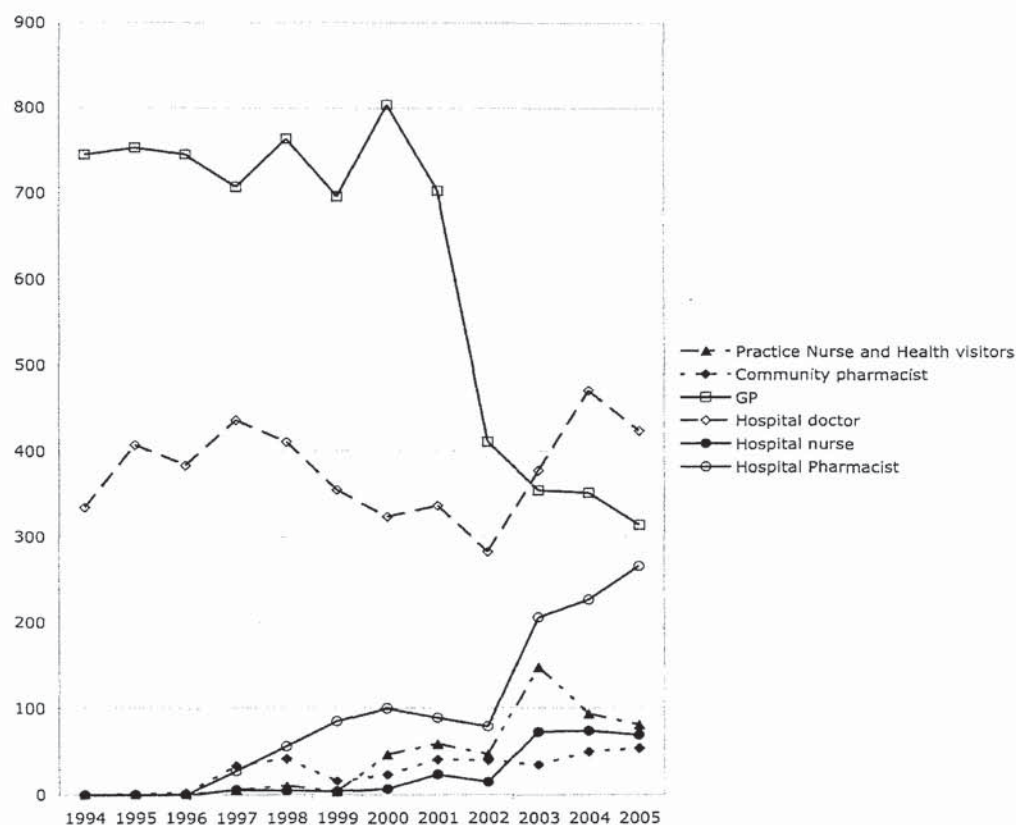
Figure 5-2 : Influence of bypass reports on West Midlands ADR reporting trends from 1997 to 2005



Because details of bypass reports are limited, these reports were not included in the further analysis of ADR reporting in the West Midlands. West Midlands ADR reporting data (excluding bypass data and meningitis C vaccine reports) was further analysed in the present study in order to investigate the possibility of trends in ADR reporting for the various groups

of healthcare professionals. Figure 5-3 depicts the number of ADR reports per year by healthcare professional group.

Figure 5-3 : Reporting trends by healthcare profession in the West Midlands 1994 to 2005 (excluding meningitis C vaccine reports)



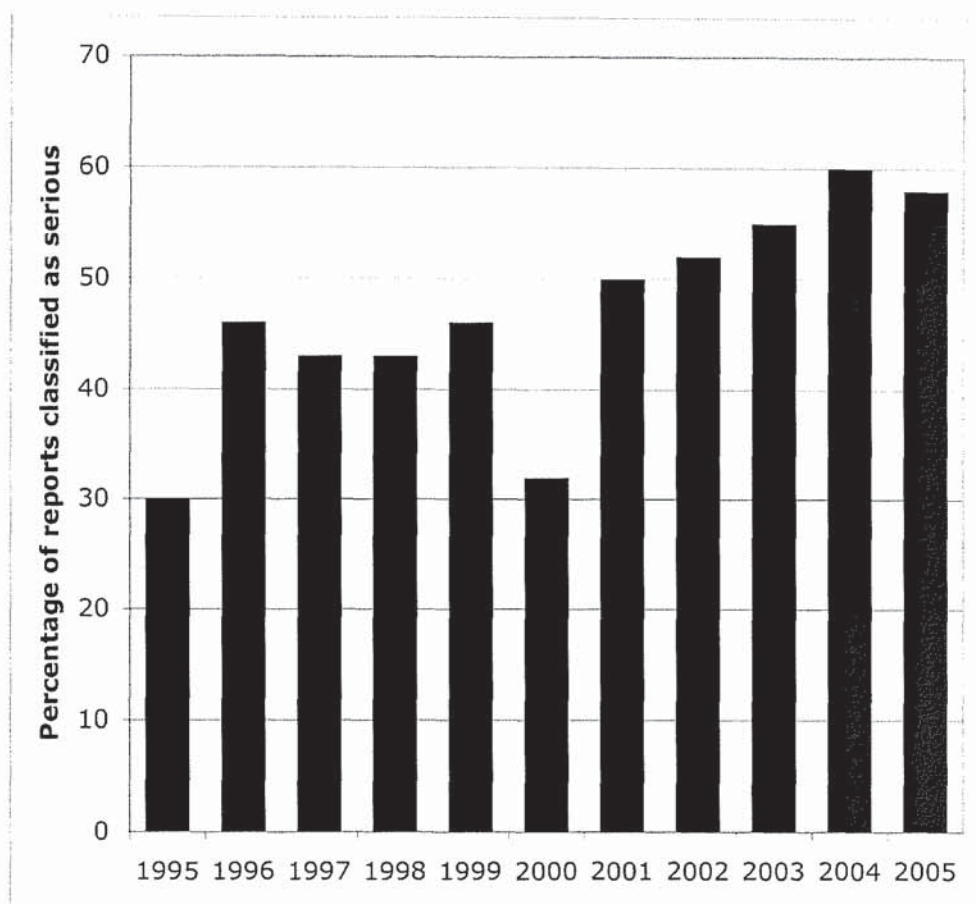
Both nurse and pharmacist ADR reporting have undergone gradual increases since, and even prior to, their formal admittance to the reporting scheme (1997 and 2003 respectively). Hospital doctors have remained a substantial source of ADR reports. General practitioners have been historically the highest reporting group in the region in absolute numbers of reports, but since 2002 a marked decline in their reports has occurred (Table 5-1). Compared to 1994, 2005 has 57.85% fewer ADR reports from general practitioners.

Table 5-1 : General Practitioner ADR reporting to the West Midlands Centre for Adverse Drug Reaction Reporting from 1994 to 2005

Year	Number of reports	Percentage change
1994	745	Not available
1995	753	1.07
1996	745	-1.06
1997	707	-5.10
1998	764	8.06
1999	696	-8.90
2000	804	15.52
2001	703	-12.56
2002	411	-41.54
2003	355	-13.63
2004	352	-0.85
2005	314	-10.80

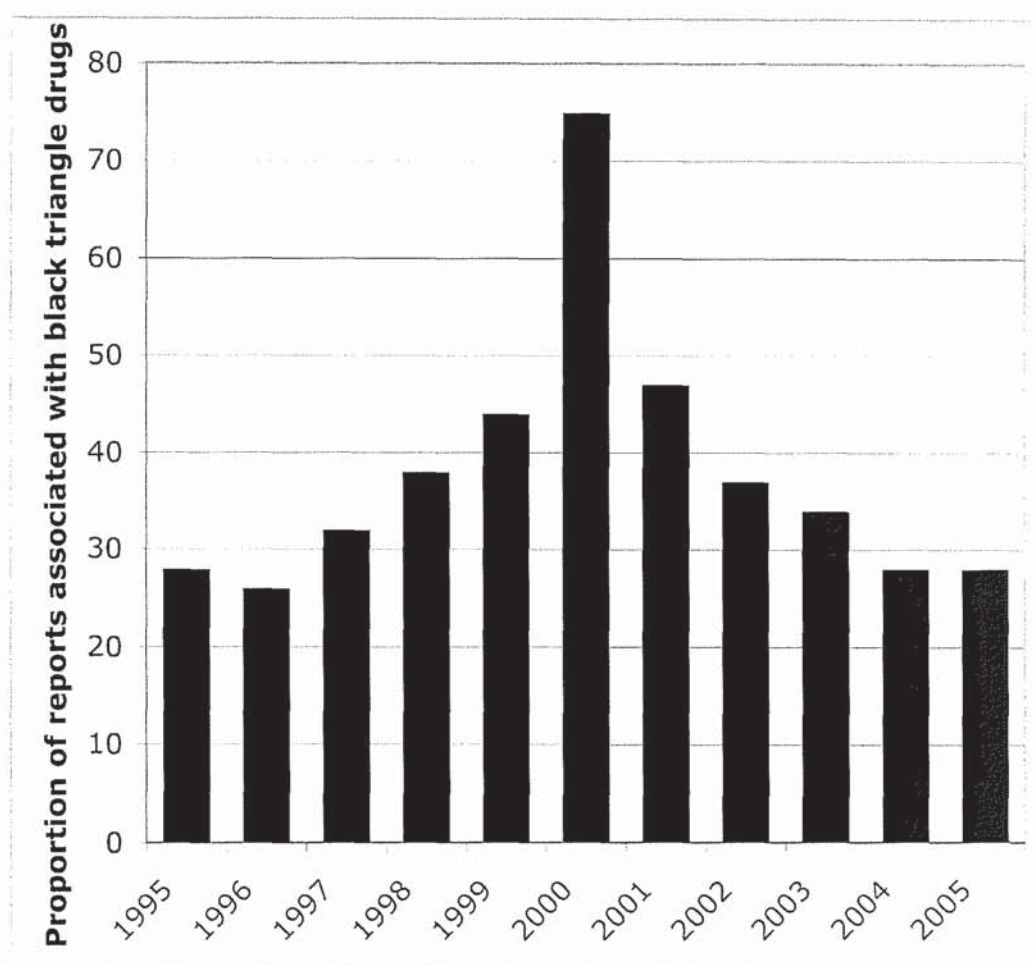
An analysis of the percentage of reports concerning ADRs of a serious nature was undertaken by extracting the proportion of reports that were serious from West Midlands YCC annual reports. Serious reports were defined as those considered as serious reactions by the criteria of the MHRA. Data was available from 1995 to 2005. This included reports from the meningitis C vaccination campaign. Over that ten-year period the percentage of serious ADR reports, submitted by all reporters, was maintained above 30% except in 1995 and 2000 (Table 5-4 overleaf) There is a possible trend towards more a higher proportion of serious reactions in later years.

Figure 5-4 : Proportion of ADR reports classified as serious received by the West Midlands Centre for Adverse Drug Reactions from 1995 to 2005



The proportion of ADR reports that were related to black triangle drugs was extracted from the West Midlands CSM annual reports. Data was available from 1995 to 2005. This included reports from the meningitis C vaccination campaign. **Figure 5-5** illustrates the variability of the proportion of black triangle drugs reported to the West Midlands Centre for adverse drug reactions. There is no clear trend in the reporting to black triangle drugs, although there is a notable spike in the year 2000.

Figure 5-5 : The proportion of ADR reports associated with black triangle drugs received by the West Midlands Centre for Adverse Drug Reactions from 1995 to 2005



To assess the differences in reporting between healthcare professional groups, the proportions of serious and black triangle drug reports reported by each group was obtained from the West Midlands YCC's annual reports. For the purposes of comparison, reports related to meningitis C vaccine during 1999, 2000 and 2001 were excluded from this analysis. Data was available for different healthcare professional groups for varying periods of time (Table 5-2). Mean percentages have been calculated over the number of years reports were available for.

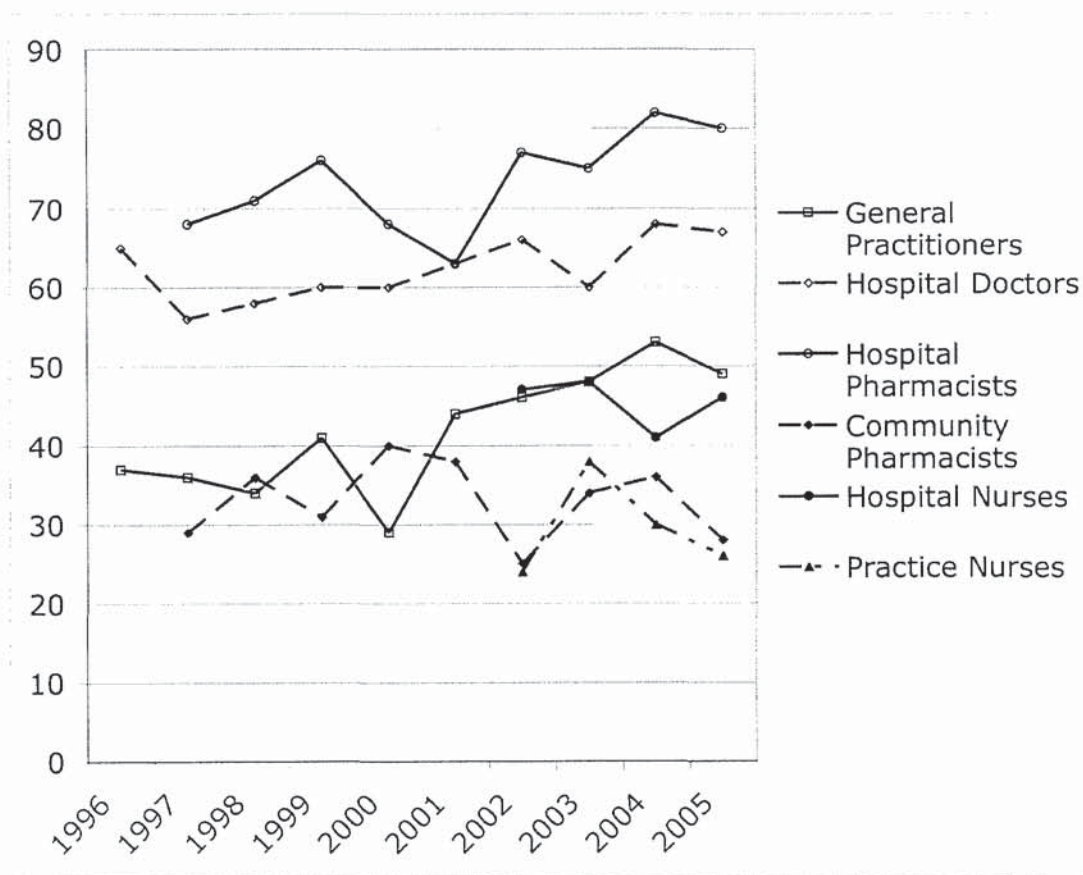
Hospital based practitioners of all professional groups reported more serious reactions than those based in primary care. In primary care, general practitioners reported the highest proportion of serious adverse drug reactions.

Table 5-2 : Average proportions of reports classified as serious by healthcare professional group

Professional group	Percentage of reports classified as serious
Hospital Doctors 1996 to 2005	62.30
Hospital Pharmacists 1997 to 2005	73.33
Hospital Nurses 2002 to 2005	45.50
General Practitioners 1996 to 2005	41.70
Community Pharmacists 1997 to 2005	33.00
Practice Nurses 2002 to 2005	29.50

The proportion of serious reports varied by year for each professional group Figure 5-6.

Figure 5-6 : Proportion of serious reports by professional group from 1996 to 2005



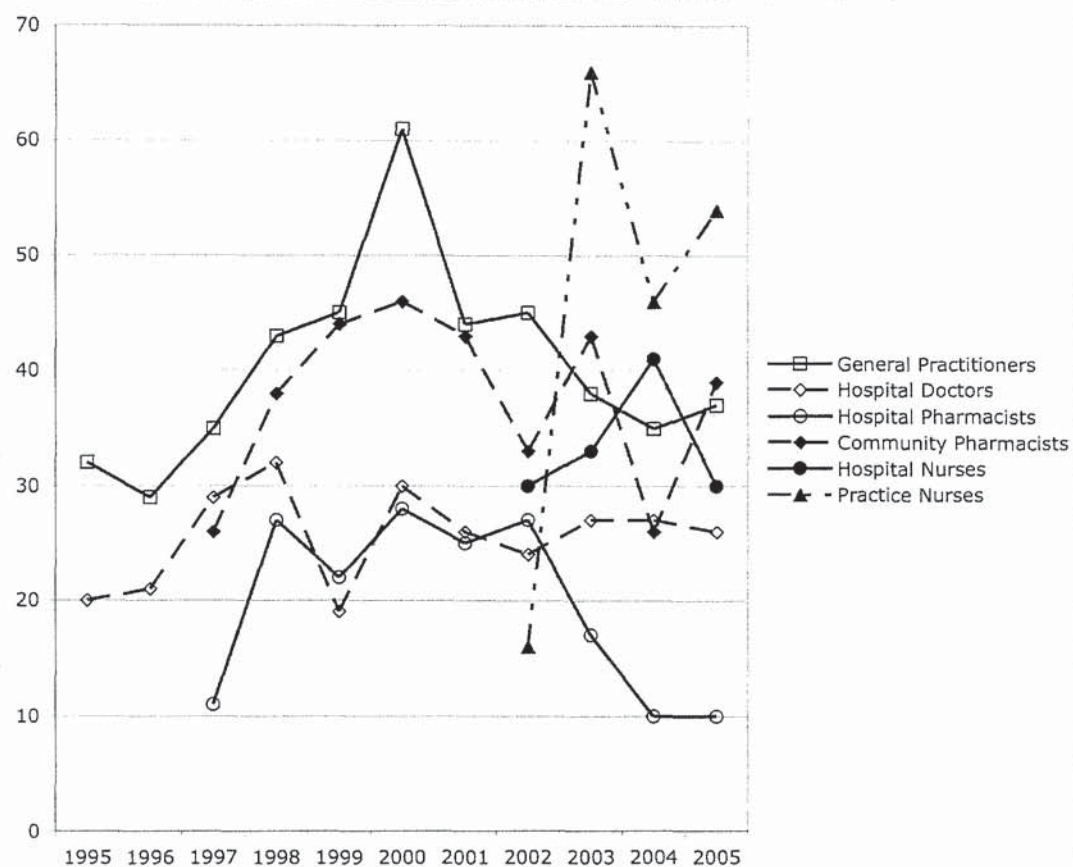
There was variation in the proportion of black triangle reports made by different healthcare professional groups Table 5-3. To avoid the disproportionate effect of ADR reports concerning meningitis C vaccination, these have been excluded from this analysis. Healthcare professional groups in primary care were responsible for higher proportions of reports related to black triangle drugs. Within the hospital sector nurses were responsible for the highest proportion of black triangle drug reports.

Table 5-3 : Average proportions of reports related to black triangle drugs made by healthcare professional groups

Healthcare professional group	Percentage of reports related to black triangle drugs
Hospital Doctors 1995 to 2005	25.55
Hospital Pharmacists 1997 to 2005	19.67
Hospital Nurses 2002 to 2005	33.50
General Practitioners 1995 to 2005	40.36
Community Pharmacists 1997 to 2005	37.56
Practice Nurses 2002 to 2005	45.50

The proportion of black triangle reports varied by professional group by year (Figure 5-7 overleaf). It is noticeable that hospital doctors and hospital pharmacists report the lowest proportion of ADR associated with black triangle drugs.

Figure 5-7 : Proportion of black triangle drug reports per year made by healthcare professional groups between 1995 to 2005

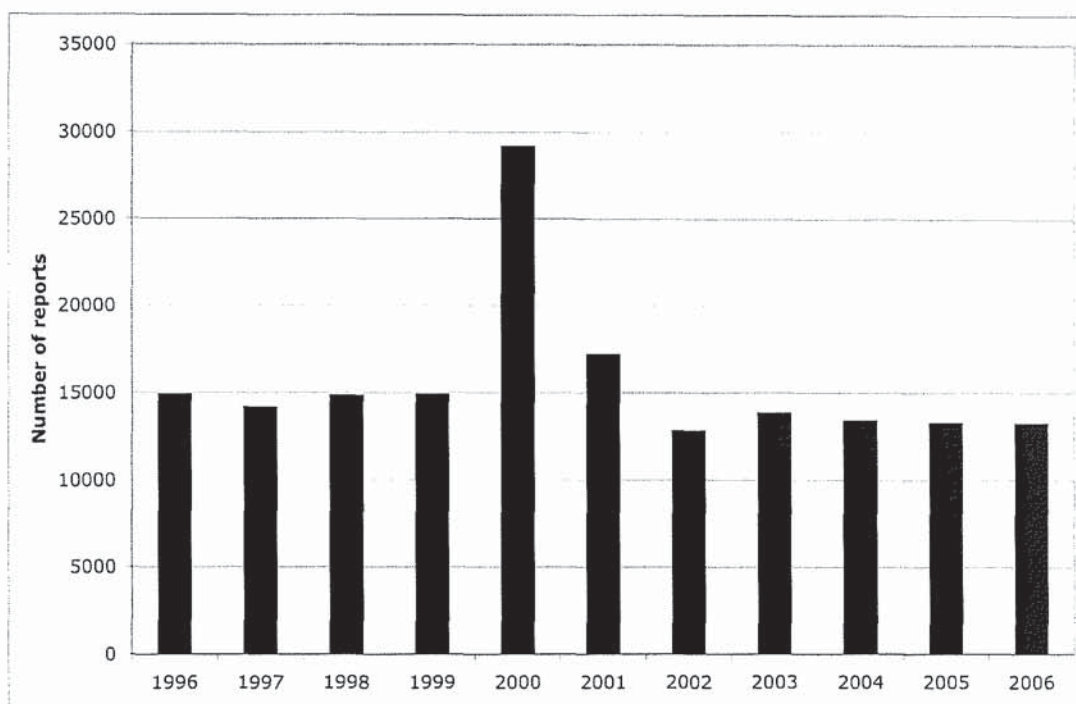


5.1.1. Comparison of West Midlands ADR reporting with national ADR reporting trends

5.1.1.1. National MHRA data

Data on adverse drug reaction reporting was obtained from the MHRA under the Freedom of Information Act 2004 for the years 1996 to 2006. Yearly total numbers of reports received by the Yellow Card scheme are depicted in Figure 5-8. In 2000, and to a lesser extent 2001, reports were higher than would be predicted owing to the meningitis C vaccination campaign operative at that time.

Figure 5-8 : Yellow Card reports from 1996 to 2006 made to the MHRA



Recent years have seen a fall in the number of reports, although the fall is gradual Table 5-4.

Table 5-4 : Percentage falls in total ADR reporting over the 2004 to 2006 period

Year	Number of reports	Percentage fall from previous year
2004	13462	3.34%
2005	13350	0.83%
2006	13151	1.49%

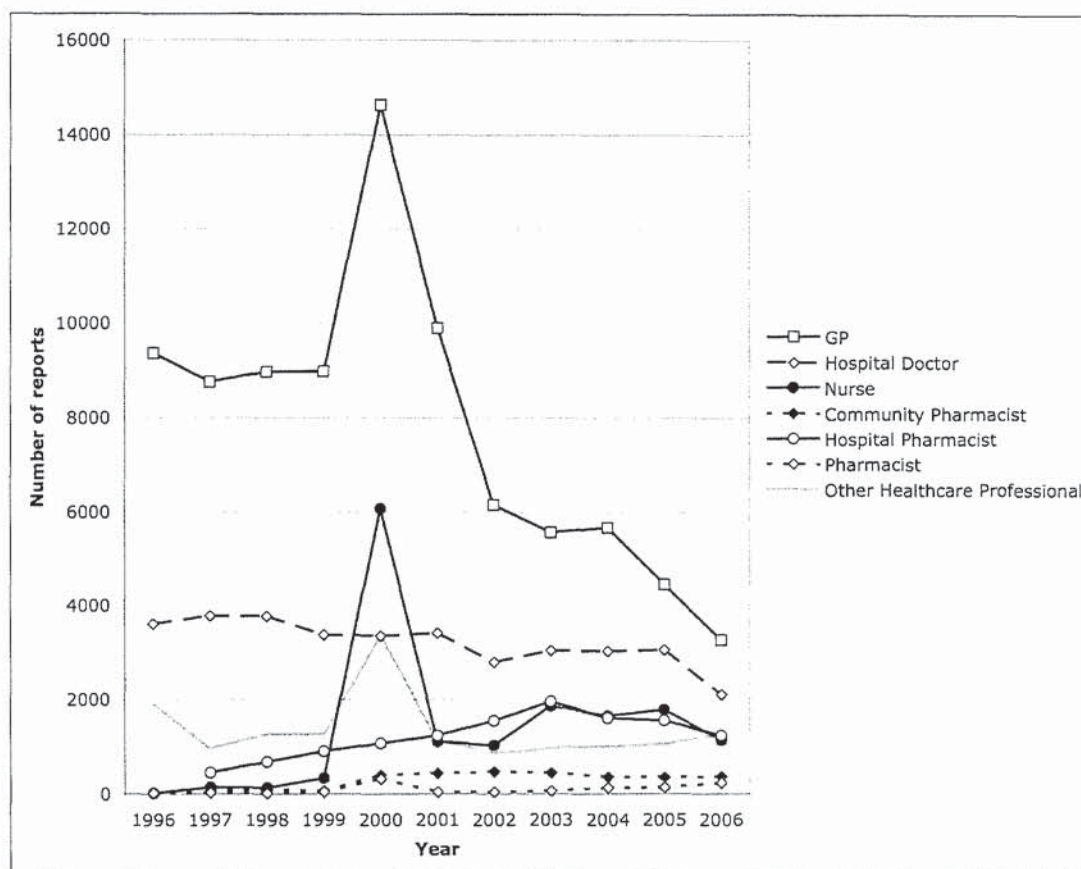
In 2006 there was a large increase in reports received directly from patients. After removal of these reports from the data, the percentage falls in ADR report was greater than 20% (Table 5-5 overleaf).

Table 5-5 : Percentage falls in healthcare professional ADR reporting over the 2004 to 2006 period

Year	Number of reports	Percentage fall from previous year
2004	13462	3.34%
2005	12398	7.90%
2006	9593	22.62%

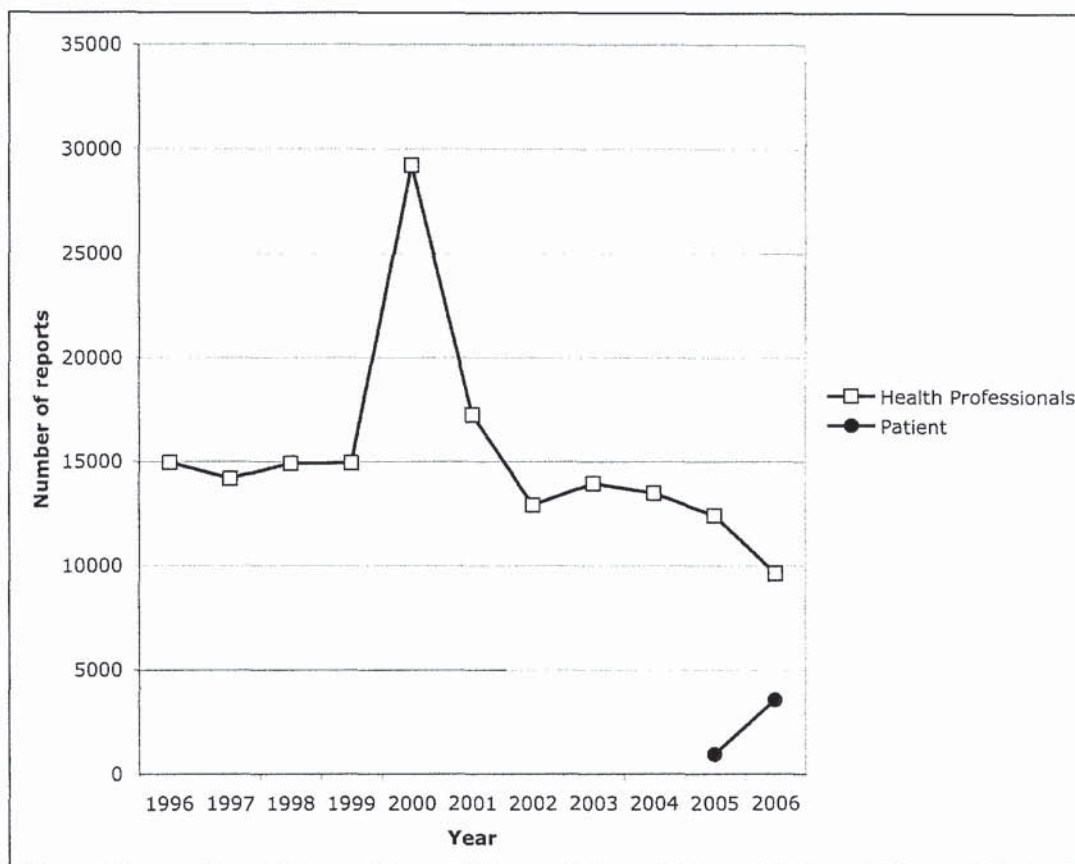
Data from the MHRA was used to create a graph of reports by health care professionals between 1996 and 2006. The MHRA make no distinction between community and hospital nurse reports. The MHRA do distinguish between hospital and community pharmacists, but in cases where the MHRA are unable to attribute an ADR report to either group these are counted in a third group called “pharmacist”. From 1996 to 1999 GP reports were greater than 8000 per year. Following the 2000 surge in reporting related to the Meningitis C vaccination programme, GP reports have been on a sustained decline, with only 3274 ADR reports in 2006 (Figure 5-9).

Figure 5-9 : Numbers of ADR reports received by profession by the MHRA between 1996 and 2006 (patient reports excluded)



In order to compare the levels of healthcare professional ADR reporting with patient reporting, all healthcare professional ADR reporting data was pooled and compared to patient reports (Figure 5-10). Patient reports accounted for 952 reports in 2005, and 3558 reports in 2006. As previously noted in Table 5-5, healthcare professional reporting shows a decline in reporting in comparison to patient ADR reporting.

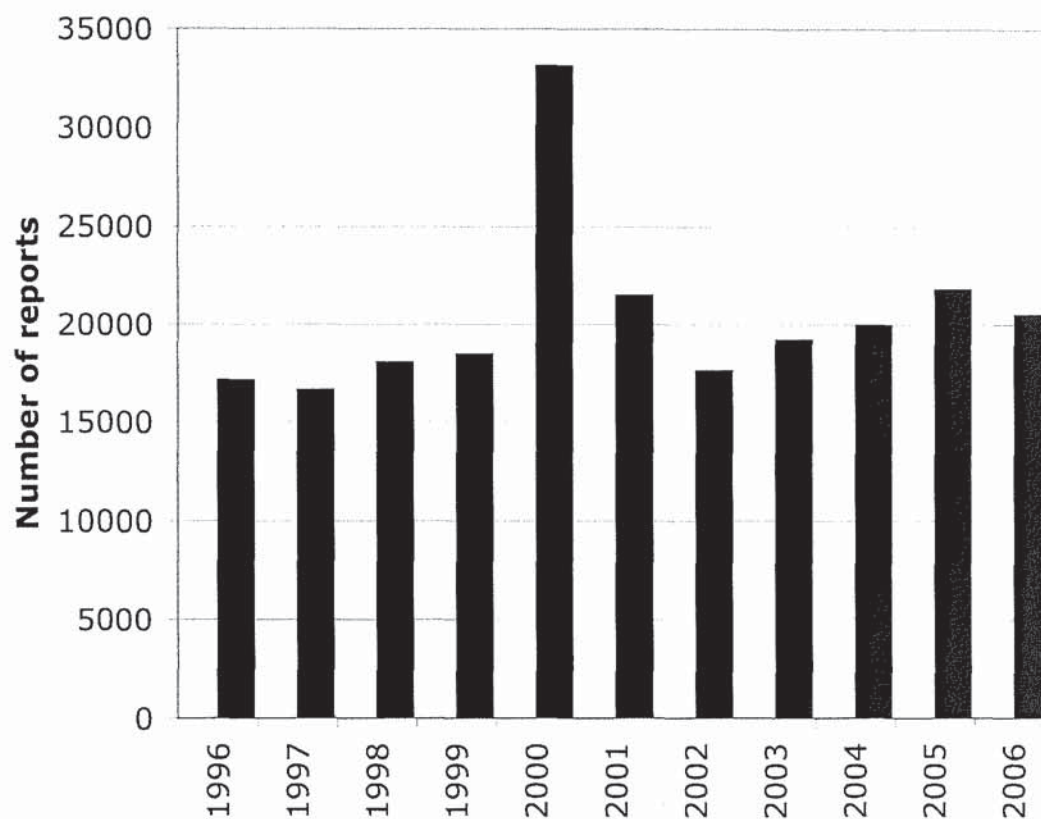
**Figure 5-10 : Number of health professional ADR reports compared to patient reports
1996 to 2006**



Healthcare professional ADR reports to the pharmaceutical industry

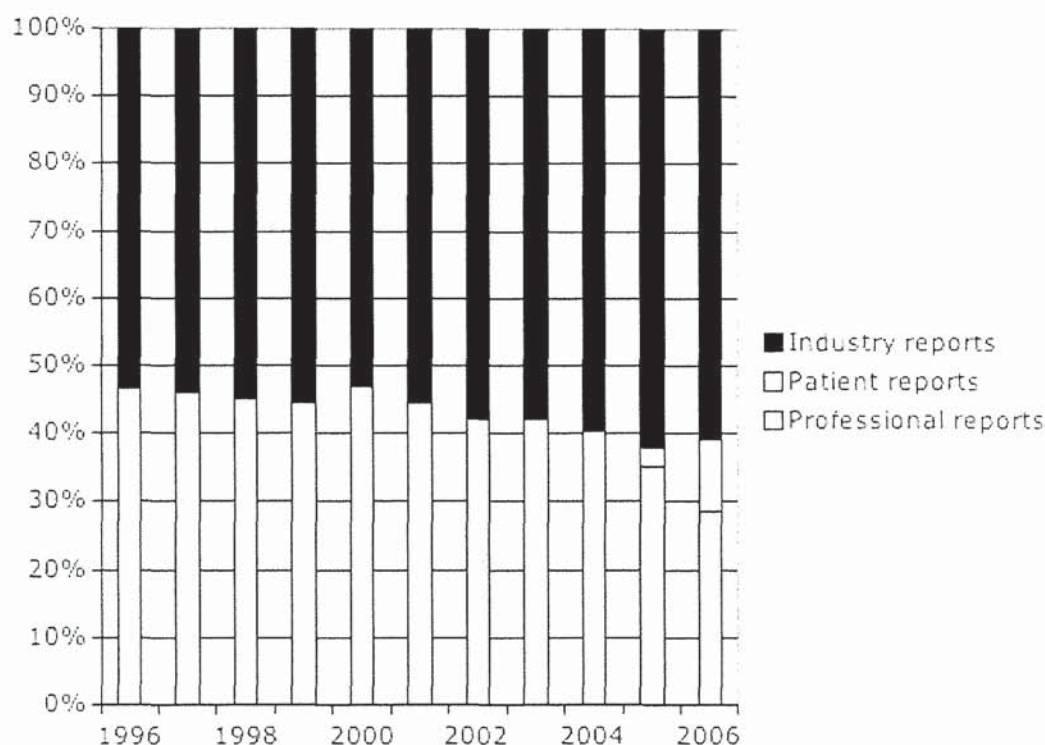
Figure 5-11 shows the numbers of ADR reports being made directly to the pharmaceutical industry – which were subsequently passed on to the MHRA. The number of reports in 2000 and 2001 is likely to have been inflated by the Meningitis C vaccination campaign. A slight trend towards higher levels of ADR reporting to industry is apparent, in contrast to falling numbers of ADR reports to the Yellow Card scheme as seen in Figure 5-10.

Figure 5-11 : Industry reports from Market Authorisation holders received by the MHRA from 1996 to 2006



Data on ADR reports to the pharmaceutical industry was combined with healthcare professional ADR reports and patient ADR reports received by the MHRA to examine trends in industry reporting over a ten-year period Figure 5-12. Examination of this graph appears to indicate that direct reports to the MHRA now account for less than 30% of all reports.

Figure 5-12 : Proportion of reports obtained from industry, patients, and professionals.

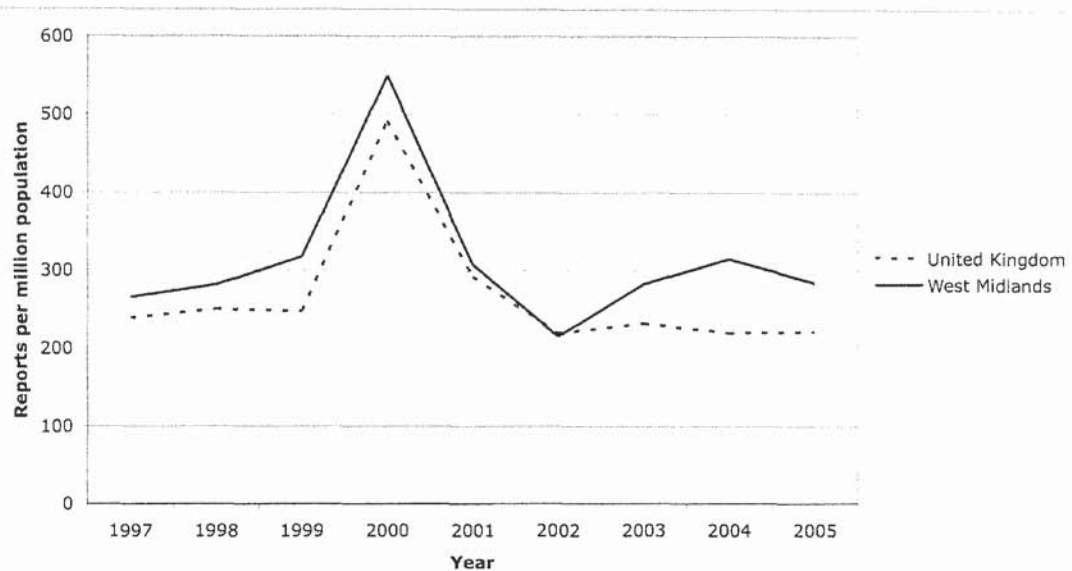


Comparison of national ADR reporting rates with West Midlands regional reporting rate

ADR reporting rates were compared between the United Kingdom and the West Midlands. The timeframe where all ADR reports were available (including bypass reports to the MHRA) were used in the present comparison (1997 to 2005). The reporting rate per million population for the West Midlands was calculated using the 2001 census population for the West Midlands (5 268 319). West Midlands' reports were subtracted from the national reporting data, and the reporting rate per million population calculated using the 2001 census population (58 789 194) for the UK, minus the West Midlands population (5 268 319). The results are presented in Figure 5-13. National rates also include reports from the other 4 regional centres. Although the West Midlands ADR reports followed national trends, the

number of ADR reports per million population was higher in the West Midlands, with the exception of 2002.

Figure 5-13 : Comparison of United Kingdom reporting rate per million population with the West Midlands reporting rate from 1997 to 2005

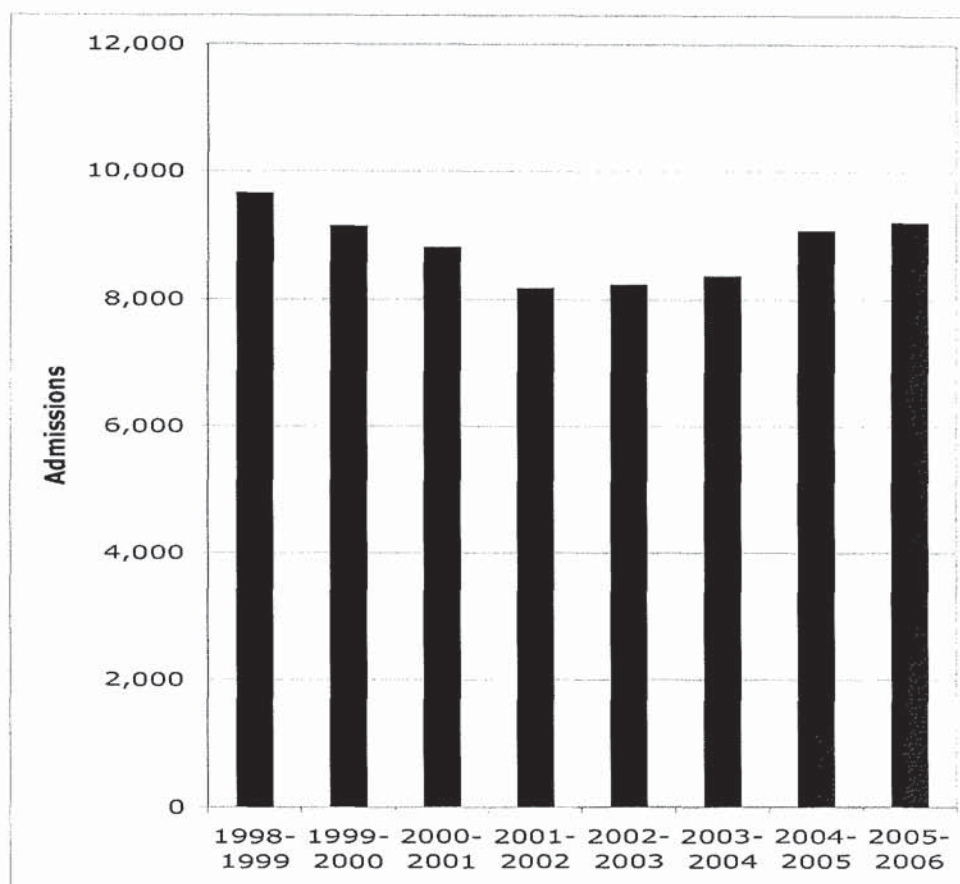


5.1.1.2. Hospital Episode Statistics relating to adverse drug reactions

Another measure of the incidence of ADRs in the UK, are Hospital Episode Statistics (HES) data. An analysis of ICD10 codes (secondary and primary) involving conditions related to adverse drug reactions was undertaken.

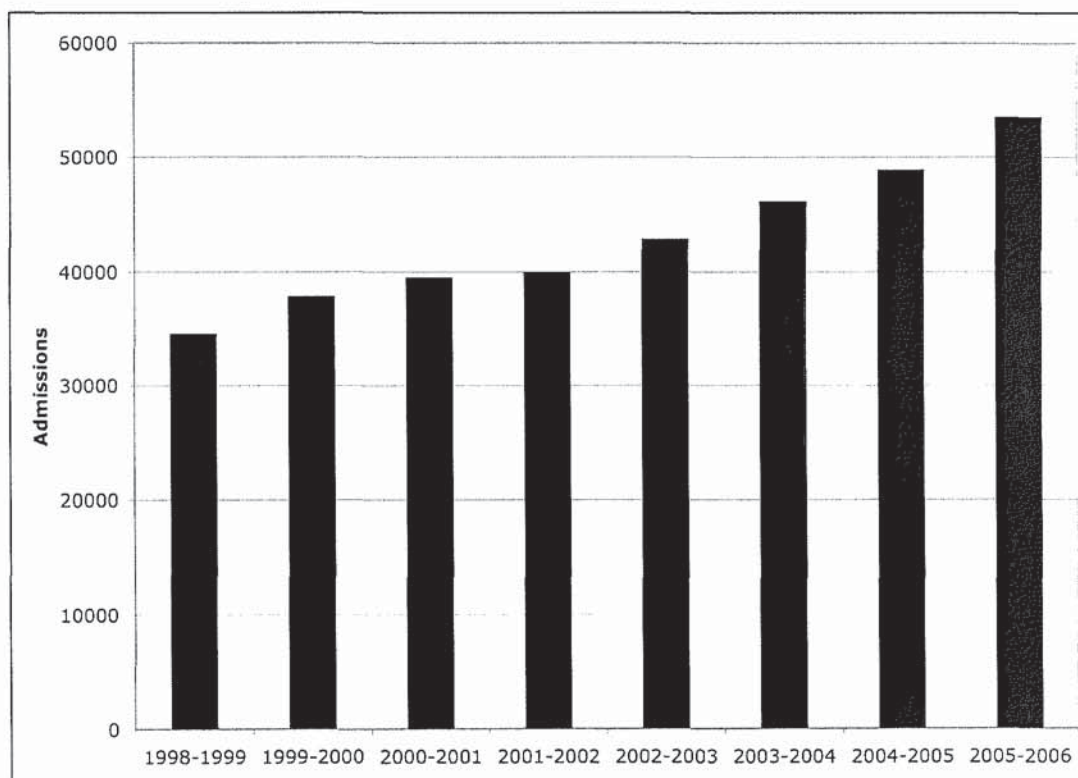
Data related to primary ICD10 codes associated with adverse drugs reactions from 1998 to 2006 was collated from 1998 to 2006 and placed in Excel (Microsoft® Excel ® 2004 for Mac). Despite a low point between 2001 to 2003, there is no clear trend for falling levels of drug-related admissions over from 1998 to 2006 (Figure 5-10).

**Figure 5-14: Admissions coded by primary ICD10 related to adverse drug reactions
1998 to 2006**



Data from 1998 to 2006 was obtained from HES online and secondary ICD10 codes Y40 to Y59 (External Cause: Drugs, medicaments and biological substances causing adverse effects in therapeutic use) were extracted into Excel (Microsoft® Excel ® 2004 for Mac). Over the eight year period covered by the data available, the numbers of admissions coded with ICD 10 codes T40 to Y59 increased from 34,578 per year to 53,632 which was a 55% increase (Figure 5-15 overleaf).

Figure 5-15 : Number of admissions by financial year from secondary ICD10 codes Y40 to Y59 (External cause: Drugs, medicaments and biological substances causing adverse effects in therapeutic use)



5.2. Hospital ADR reporting in the West Midlands during 2004-2006

A detailed examination of hospital adverse drug reaction reporting was performed using the West Midlands Centre for Adverse Drug Reaction database. Data analysed was from financial years 2004-2005 and 2005-2006.

The total number of reports received submitted from NHS trusts in the West Midlands was 1748, forty-nine (2.8%) of which were fatal. Nineteen percent of reports (334) were concerned with black triangle drugs.

The top ten drugs reported by acute NHS trusts are presented in Table 5-6 and top ten black triangle drugs are presented in Table 5-7.

Table 5-6 : Top ten reported drugs from acute NHS Trusts during 2004-2006

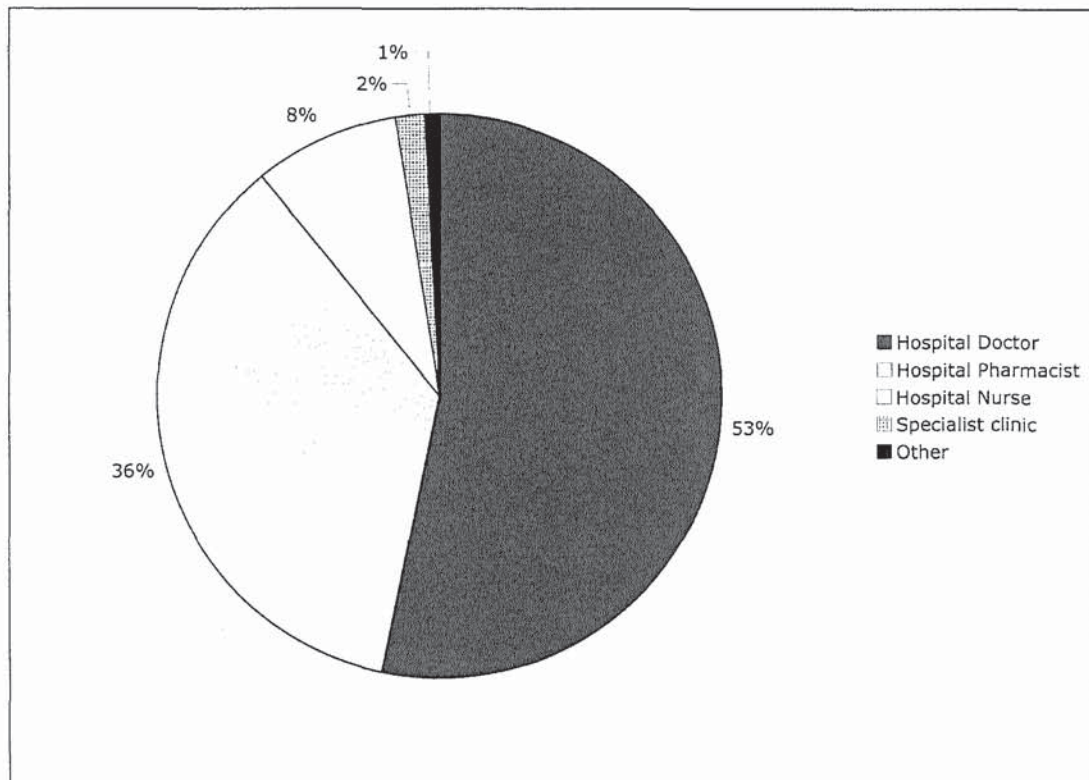
Drug name	Number of reports	Percentage of total reports
aspirin	86	4.9
infliximab▼	47	2.7
diclofenac	41	2.3
etanercept▼	39	2.2
adalimumab▼	27	1.5
warfarin	25	1.4
atenolol	24	1.4
bendrofluazide	24	1.4
furosemide	24	1.4
ibuprofen	24	1.4

Table 5-7 : Top ten reported black triangle ▼ drugs from acute NHS Trusts during 2004-2006

Drug Name	Number of reports	Percentage of total black triangle reports
infliximab▼	39	11.7
etanercept▼	32	9.6
adalimumab▼	24	7.2
insulin glargine▼	15	4.5
leflunomide▼	14	4.2
rosiglitazone▼	13	3.9
etoricoxib▼	12	3.6
pregabalin▼	11	3.3
atomoxetine▼	8	2.4
duloxetine▼	8	2.4

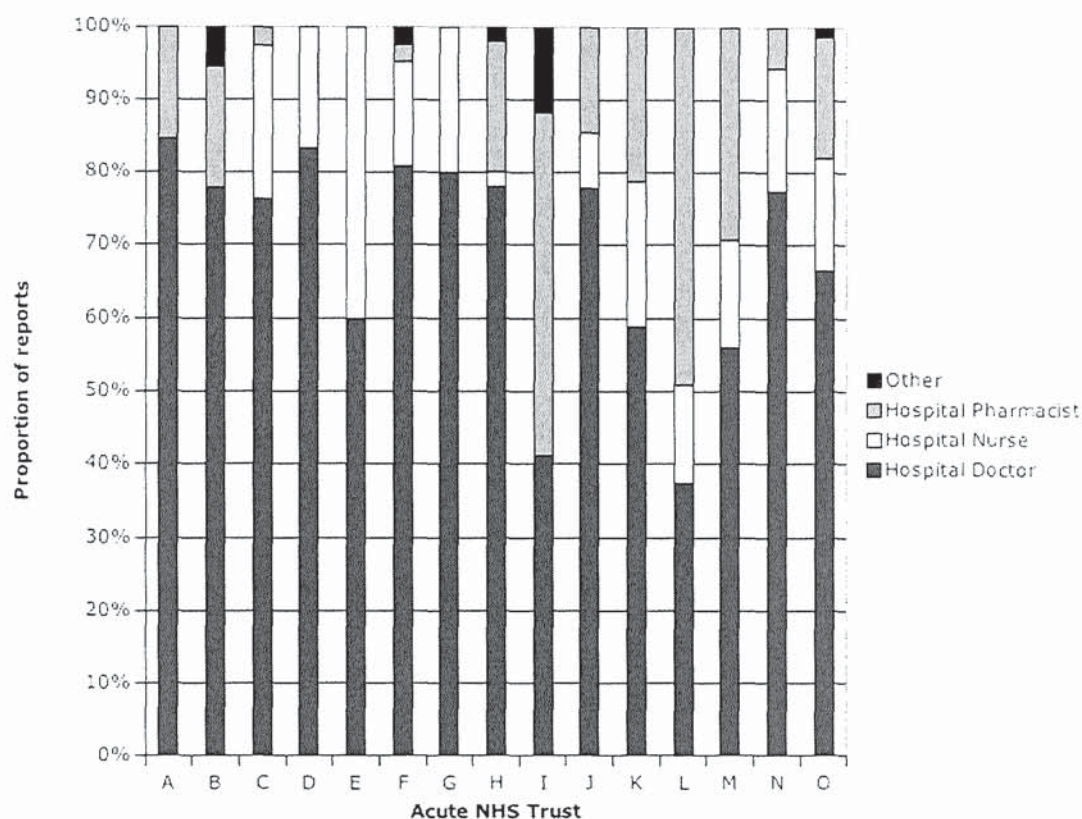
Hospital doctors submitted the highest proportion of reports from hospitals, followed by hospital pharmacists (Figure 5-16).

Figure 5-16 : Proportions of reports from professional groups received from acute NHS trusts during 2004 to 2006



The proportions of ADR reports submitted by various healthcare professional groups varied between NHS Trusts (Figure 5-17 overleaf). NHS Acute Trusts are represented by an alphabetic code, in order of hospital activity based on number of admissions per year. The NHS trust where the regional reporting centre was based is not included in this analysis, since its reporting profile is atypical owing to the presence of the Yellow Card centre.

Figure 5-17 : Proportions ADR reports from various healthcare professional groups within NHS acute trusts in the West Midlands Strategic Health authority between 2004 and 2006



Examination of the number of reports submitted by individuals from the two main reporting professions, hospital pharmacists and hospital doctors, within acute NHS Trusts showed a strong difference in the “spread” of reporting (Table 5-9). The majority of hospital doctor reported was carried out by individuals who submitted 1 to 5 cards over the two-year period.

In contrast, pharmacist was heavily skewed to a small number of very active ADR reporters, 9 individuals being responsible for 61% of all ADR reports in the West Midlands.

Table 5-8 : The spread of reporting amongst hospital pharmacists and hospitals doctors

	Hospital Pharmacists		Hospital Doctors	
Number of ADR reports	Number of reporters (% of total reporters)	Number of ADR reports (% of total reports)	Number of reporters (% of total reporters)	Number of ADR reports (% of total reports)
>10 reports	9 (8.5%)	275 (61%)	6 (1.3%)	161 (20.8%)
6-10 reports	7 (6.6%)	41 (9.2%)	5 (1.1%)	37 (4.8%)
1-5 reports	90 (85%)	132 (29.5%)	450 (97.6%)	574 (74.4%)
Totals	106	448	461	772

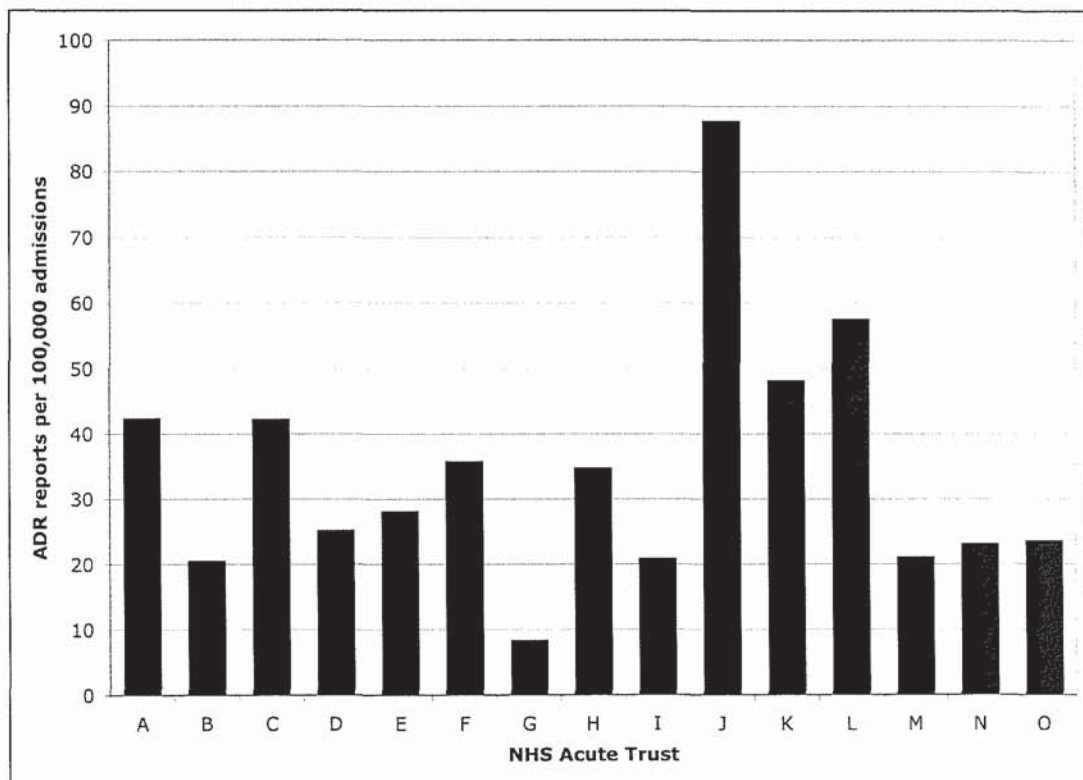
5.2.1. Hospital activity and ADR reporting.

The hospital where the regional reporting centre was based, was excluded from further analysis and comparison of hospitals sites, because of the special circumstances, which meant it was responsible for 879 reports (50.3%) of the total 1748 reports. An outlier of this size would skew any further analysis. Mental health trusts, ambulance trusts, and reports from private hospitals were also removed from further analysis (total reports 97 (5.5%)), as they were not comparable secondary care institutions. The ADR reporting performance of the remaining 14 NHS Acute Trusts in West Midlands were then compared. Acute NHS trust reporting rates per 100,000 admissions varied between sites in the region. The mean rate was found to be 35 reports per 100,000 admissions (Range 8 to 88, median 28).

Hospital trusts were allocated a code (A to O) in order to maintain anonymity. Data is presented in Figure 5-18 in order of ascending trust admission activity

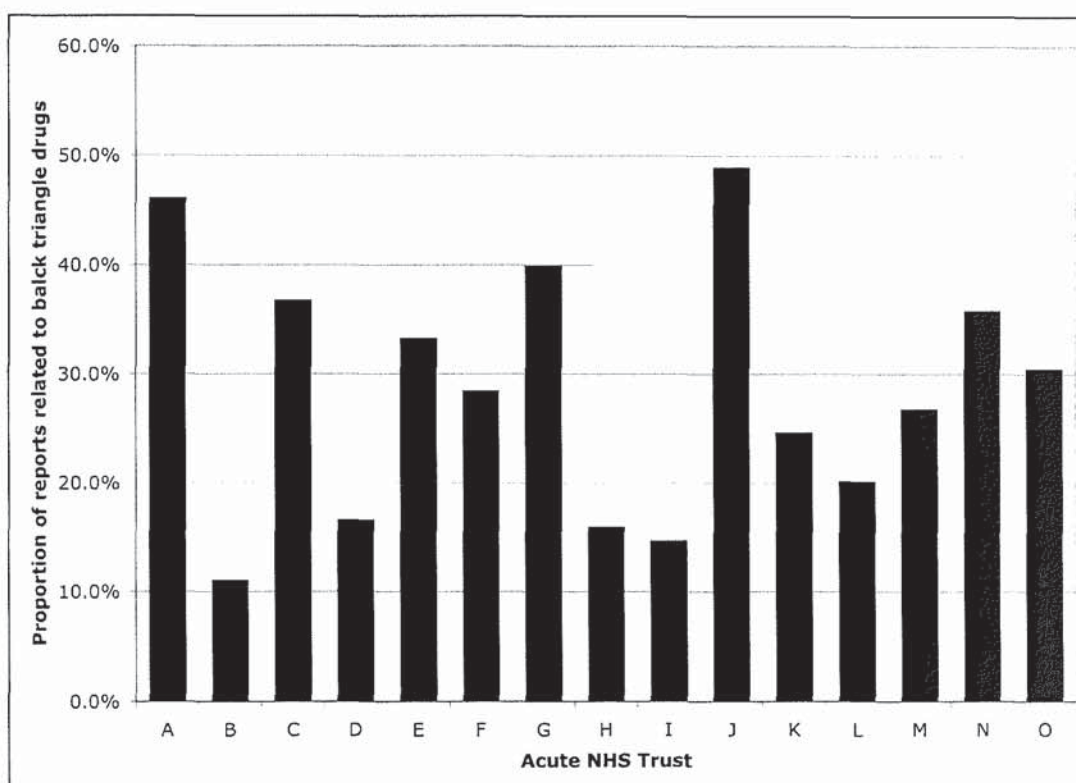
For purposes of comparison, the hospital containing the regional reporting centre maintained a reporting rate of 380 reports per 100,000 admissions, over ten times higher than the regional average, and four times higher than the best performing Acute NHS Trust. Hospital activity appeared to have no direct relationship with ADR reporting rates.

Figure 5-18 : ADR reporting rate per 100,000 admissions of NHS Acute Trusts in ascending order of hospital activity between 2004 and 2006



The proportion of ADR reports to black triangle drugs varied between acute NHS trust sites (Figure 5-19). The mean percentage was 28.7% (range 11.1 to 49.0%). The proportion of black triangle reports at the YCC site was 9.2%.

Figure 5-19 : Proportion of ADR reports related to black triangle drugs by NHS Acute Trusts in ascending order of hospital activity



5.2.2. Correlation between hospital adverse drug reaction reporting rates and medicine management performance indicators.

Acute NHS hospital Trusts data on medicines management performance, published by the Healthcare Commission in 2005/2006, was compared with information on ADR reporting rates for the period 2004 to 2006.

This was analysed using SPSS (SPSS for Windows, Rel. 12.0.1. 2003. Chicago: SPSS Inc.). As all Healthcare commission data was non-parametric ordinal data, Spearman's ranking correlation was used to test for a correlation between and the number of reported ADRs per 100,000 admissions. Results are displayed in Table 5-9.

Table 5-9 : Relationship between Healthcare Commission 2005/2006 medicines management performance indicators and ADRs reported per 100,000 admissions

Medicines Management 2005/2006 Indicator	Statistical outcome
Overall Medicines Management Performance	$r_s = -0.002$ p (two-tailed) = 0.995
Indicator 2: patients on more than 4 medicines receiving a comprehensive medication review	$r_s = -0.254$ p (two-tailed) = 0.361
Indicator 10: pharmacy contribution per inpatient seen	$r_s = -0.212$ p (two-tailed) = 0.449
Indicator 16: clinical pharmacy time available per inpatient admission	$r_s = -0.029$ p (two-tailed) = 0.919
Indicator 20: percentage time spent on clinical activity (pharmacists and technicians)	$r_s = -0.228$ p (two-tailed) = 0.420

None of the indicators examined showed any relationship with ADR reporting rates within acute NHS trusts in the West Midlands region.

5.3. Primary Care Trust ADR reporting during the 2004 to 2006 period

The West Midlands Region is covered by the West Midlands Strategic Health Authority. During the period 2004 to 2006, the region comprised of thirty PCTs. The estimated 2004 population of the region was 5,268,319, similar to that of Scotland (2001 Census, population size 5,064,200). The average PCT population in the West Midlands was 177,860 (range 87,900 to 366,800, median 164 950).

5.3.1. Primary Care Trust ADR reporting demographics

During the financial years 2004-2005 and 2005-2006 a total of 933 reports were made to the YCC from primary care. There were 14 reports of fatalities associated with ADRs. The top ten drugs for each financial year are presented in Table 5-10 and Table 5-11. Vaccines were excluded from these tables because they are supplied centrally. In addition, etanercept was

excluded because it requires specialist administration in hospital and was not likely to have been prescribed in primary care.

Table 5-10 : Top ten reported drugs April 1st 2004 to March 31st 2005 (excluding vaccines)

Drug	Number of reports
ezetimibe▼	18
simvastatin	18
bupropion▼	16
pregabalin▼	16
etoricoxib▼	15
rofecoxib▼	14
escitalopram▼	12
rosiglitazone▼	12
rosuvastatin▼	12
duloxetine▼	11

Table 5-11 : Top ten reported drugs April 1st 2005 to March 31st 2006 (excluding vaccines and etanercept)

Drug	Number of reports
pregabalin▼	16
strontium ranelate▼	14
escitalopram▼	12
simvastatin	11
bupropion▼	8
duloxetine▼	8
ezetimibe▼	10
tiotropium▼	8
sibutramine▼	7
solifenacin▼	7

A combined table was created for both years leading to a list of “top drugs” for the two-year period (Table 5-12). This was created for analysis of the effect of prescribing on ADR

reporting.. The total number of reports for the combined “top drugs” list (consisting of 14 drugs) was 280, which is 30% of the total number of reports. A total of 153,050,187 items were prescribed in the West Midlands during 2004-2006, the list of top drugs accounted for 5,007,259 items, which is 3.3% of all prescribing.

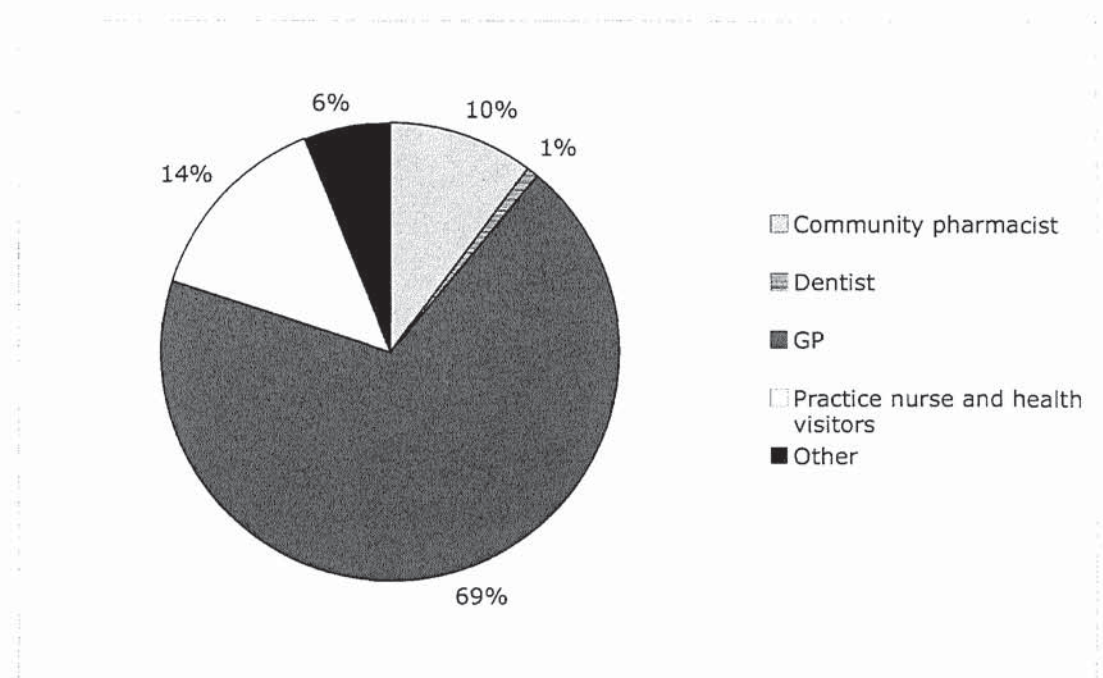
Table 5-12 : Combined ADR reports for "top drugs" for financial years 2004-2005 and 2005-2006

Drug Name	Number of reports
pregabalin▼	32
simvastatin	29
ezetimibe▼	28
bupropion▼	24
escitalopram▼	24
duloxetine▼	19
etoricoxib▼	19
rosuvastatin▼	18
rofecoxib▼	17
sibutramine▼	16
rosiglitazone▼	15
strontium ranelate▼	15
tiotropium▼	15
solifenacin▼	9

5.3.2. The reporting population

General practitioners accounted for the majority (68.9%) of reports received from Primary Care Trusts (**Figure 5-20** overleaf). Nurses (and health visitors) and pharmacists were the next highest reporting groups, producing 13.8% and 10.2% of reports respectively. The group labelled “Other” consisted of healthcare professional reports which could not be allocated to a specific professional group, for example those originating from coroners, consumer reports, and reports from specialist clinics.

Figure 5-20 : Healthcare professionals responsible for ADR reports from Primary Care Trusts in the West Midlands 2004-2006



Examination of the number of reports submitted by individual community pharmacists and GPs, within PCTs, is shown in Table 5-13. The majority of reports in both groups originate from a base of reporters who reported a maximum of 5 times in two years.

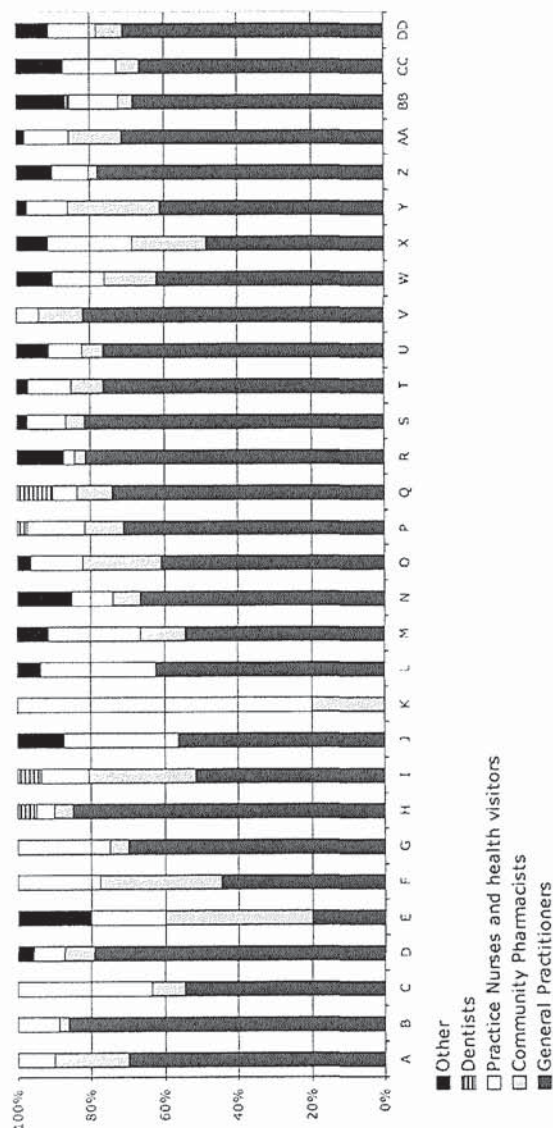
Table 5-13 : The spread of reporting amongst community pharmacists and GPs

Number of ADR reports	Community Pharmacists		GPs	
	Number of reporters (% of total reporters)	Number of ADR reports (% of total reports)	Number of reporters (% of total reporters)	Number of ADR reports (% of total reports)
>10 reports	1 (1.4%)	14 (15.4%)	2 (0.5%)	28 (4.9%)
6-10 reports	0 (0%)	0 (0%)	0 (0%)	0 (0%)
1-5 reports	71 (98.6%)	77 (84.6%)	422 (99.5%)	543 (95.1%)
Totals	72	91	424	571

Variation in the proportion of reports submitted by different healthcare professional groups was apparent between different PCTs.

Figure 5-21 shows the proportion of reports submitted by healthcare professional group in PCTs in ascending order of population size.

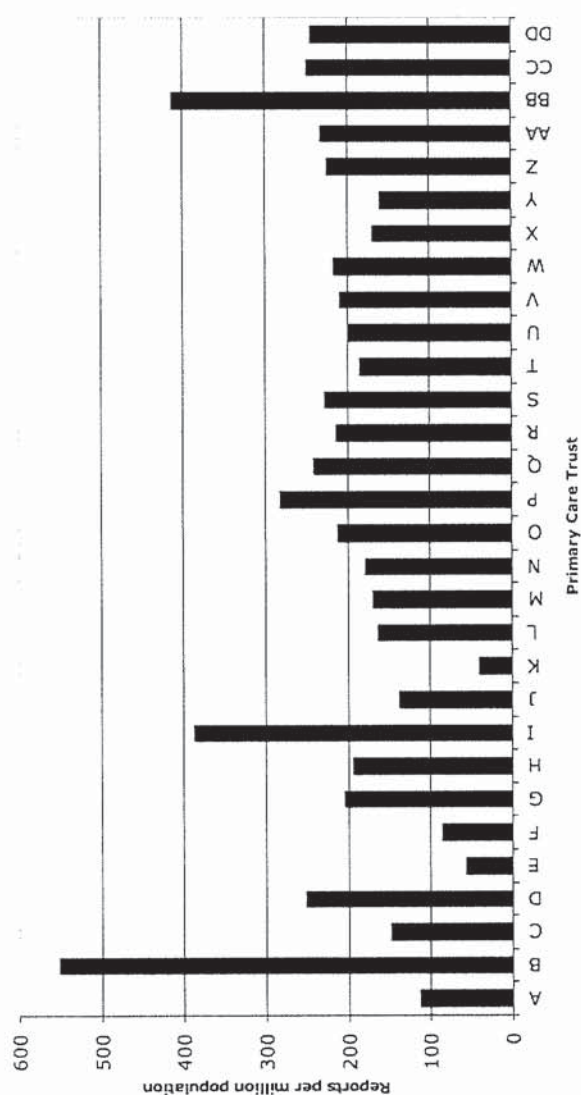
Figure 5-21 : Proportion of ADR reports submitted by healthcare profession in West Midland PCTs in ascending order of population



5.3.3. Differences between PCT reporting rates

There was variation in the ADR reporting rate between PCTs within the West Midlands region. The mean rate of reporting was 213 per million population (range 58 to 553, median 208). The reporting rate for the West Midlands PCTs is presented in **Figure 5-22** in ascending order of population size.

Figure 5-22 : ADR reporting rates for per million population during financial years 2004-2005 and 2005-2006 in ascending order of population size



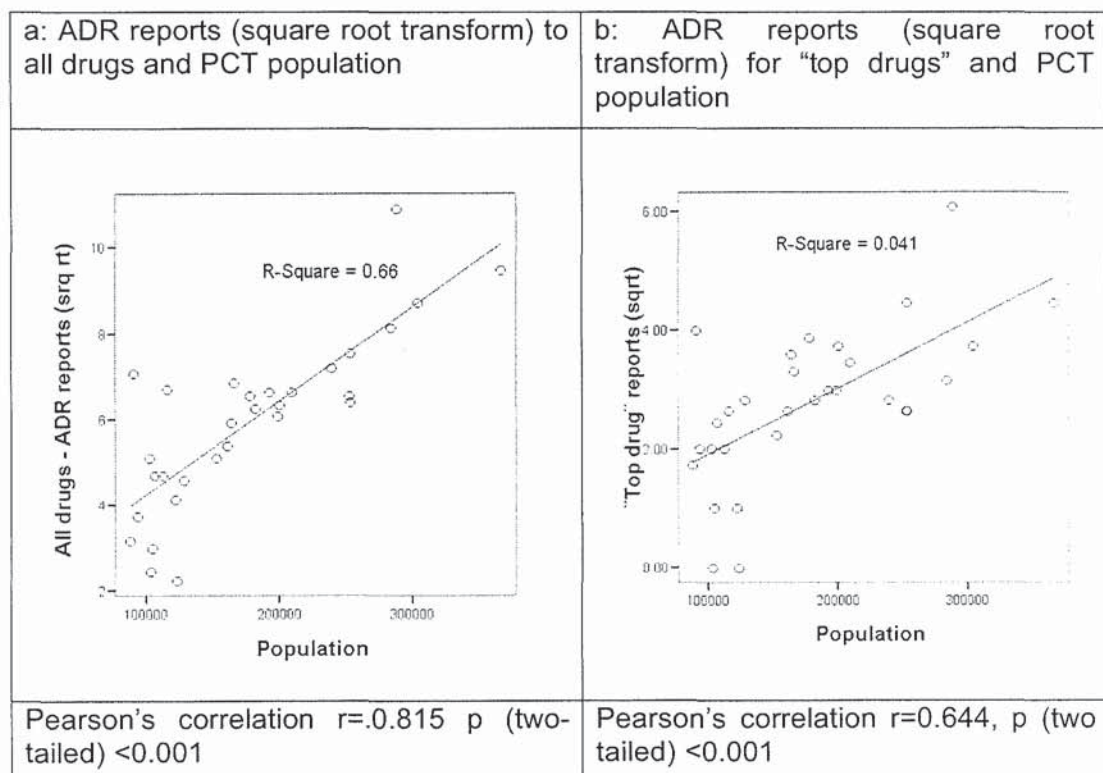
5.3.4. Testing for normality of data distributions

Before further analysis of reporting data and correlations with other data was performed, variables were tested for the purposes of deciding whether parametric or non-parametric tests could be performed using z skewness and z kurtosis and the Kolmogorov-Smirnov test. Variables initially found to be non-parametric underwent transformation and were re-tested for a normal distribution. More detailed information is available in Appendix XII.

5.3.5. Relationship between Primary Care Trust population data, primary care prescribing, and ADR reports

The number of reports associated with all drugs (square root transformation) and “top drugs” (square root transformation) was significantly associated with the 2004 population PCT populations. This justified the decision to use an ADR reporting rate per million population for further analysis to correct for the effect of population size in further analysis.

Figure 5-23 : ADR reports versus population size for West Midlands PCTs for financial years 2004-2005 and 2005-2006



Reporting related to all drugs per million population was not significantly correlated with PCT population data, Spearman's ranking correlation $r_s=.358$ p (two-tailed) <0.052 (Figure 5-24a). Reports to top ten drugs per million population (Square root +2 transformation) was not significantly correlated with PCT populations, Pearson's correlation $r= 0.202$, $P =0.285$ (Figure 5-24b).

Figure 5-24 : Adverse drug reaction reports per million population versus PCT population

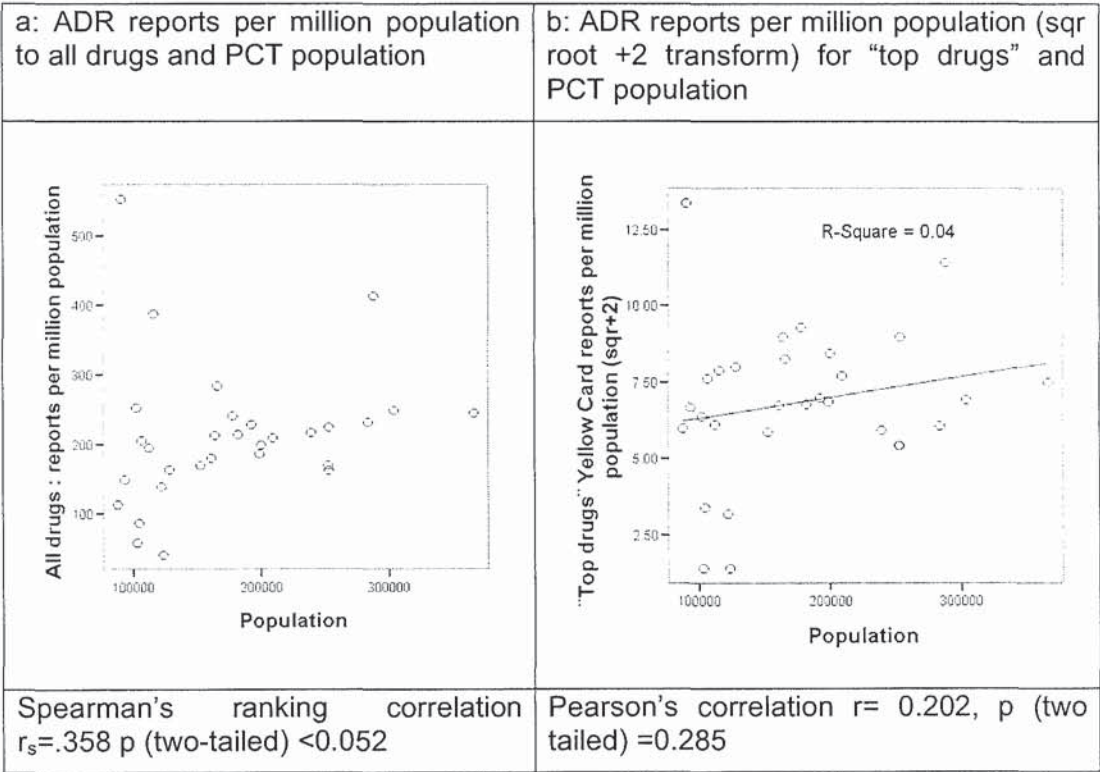
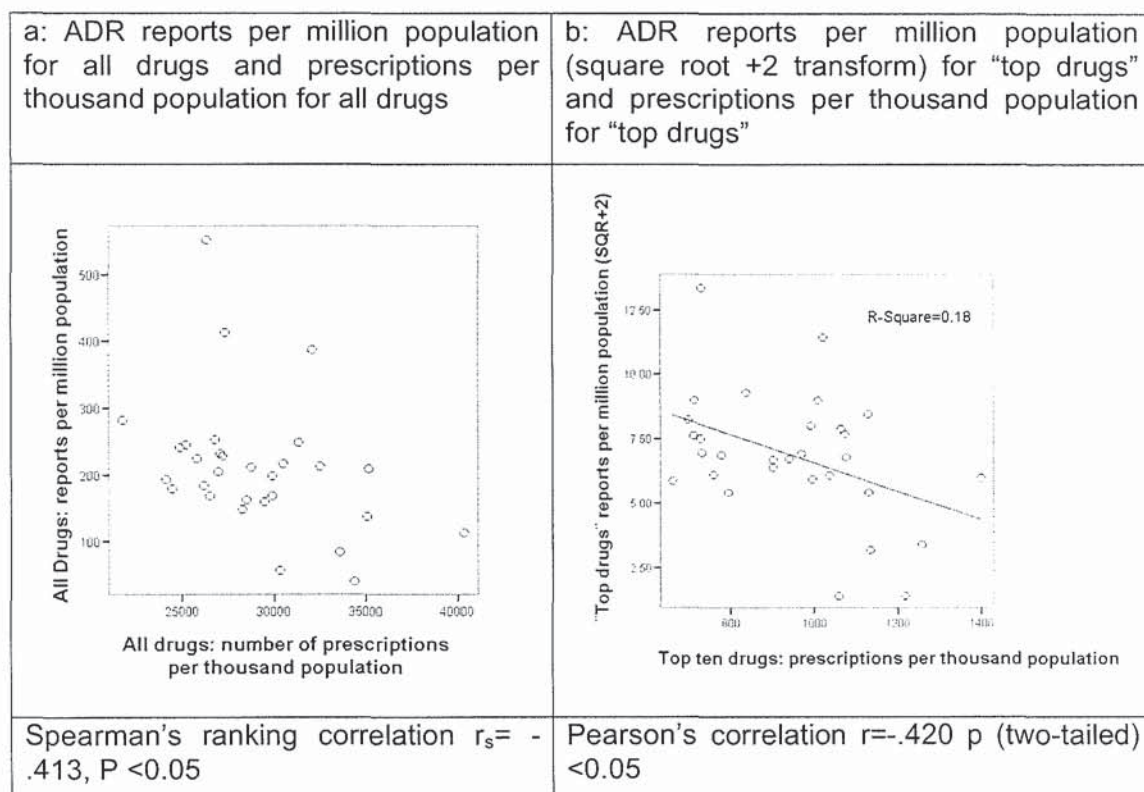


Figure 5-25 : ADR reports per million population versus number of prescriptions per thousand population in the West Midlands during financial years 2004-2005 and 2005-2006



Reports to all drugs per million population was significantly negatively correlated with the number of prescriptions issued for all drugs per thousand population (Figure 5-25a).

Reporting of “Top drugs” drugs per million population (Square root + 2 transformation) was significantly negatively correlated with the number of prescriptions per thousand population for “Top drugs” (Figure 5-25b).

5.3.6. Relationship between Primary Care Trust General Practice characteristics and Yellow Card reporting

Information relating to the characteristics of General Practice in each West Midlands PCT was obtained from The NHS Information centre. Data on the percentage of male general

practitioners, the percentage of single-handed general practitioners, the percentage of general practitioners over 55 years-of-age and the average list size of practices is presented in

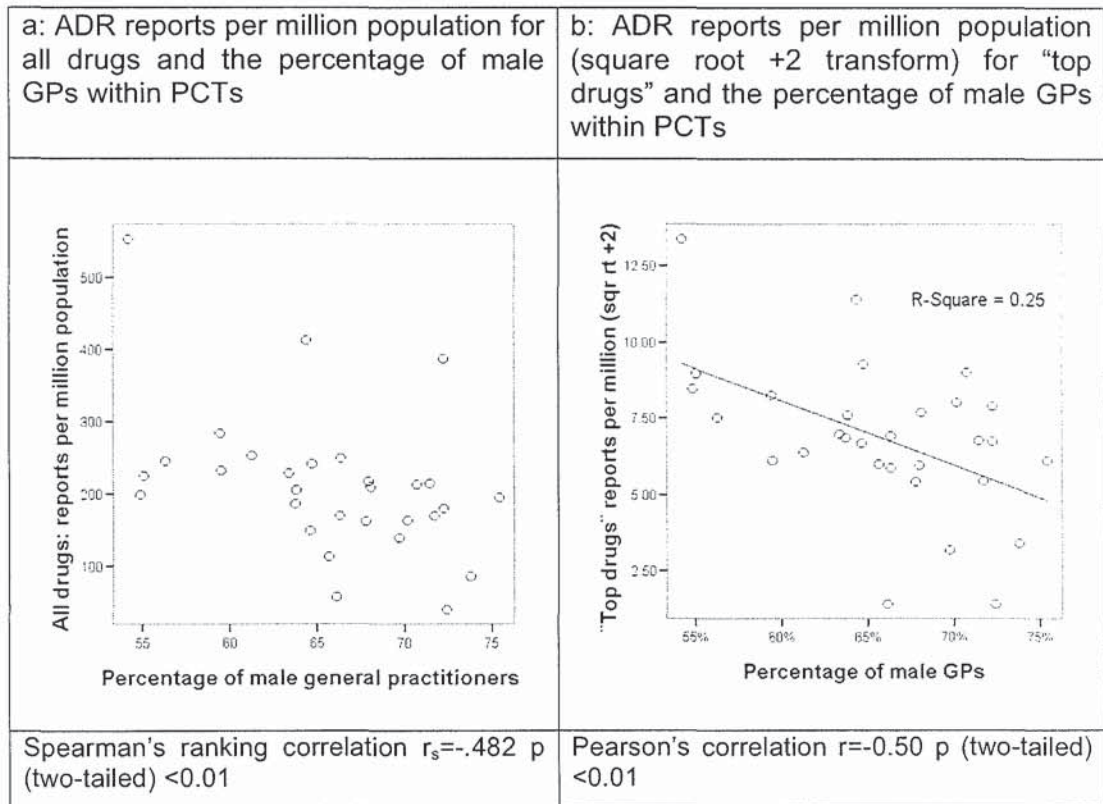
Table 5-14.

Table 5-14 : West Midlands Primary Care Trust characteristics related to General Practice

PCT characteristic	Mean (median)	Range
Percentage of male GPs	65.7% (66.2%)	54.2%-75.4%
Percentage single-handed practices	26.0% (26.29%)	0%-58.8%
Percentage of GPS over 55 years of age	22.8% (22.16%)	8%-50%
Average list size	1699 (1734)	1349-2035

Reporting of all drugs per million population was significantly negatively correlated with the percentage of male general practitioners (Figure 5-26a). The “top drugs” adverse drug reactions per million population (square root + 2 transformation) was significantly negatively correlated with the percentage of male general practitioners within a Primary Care Trust. See Figure 5-26b.

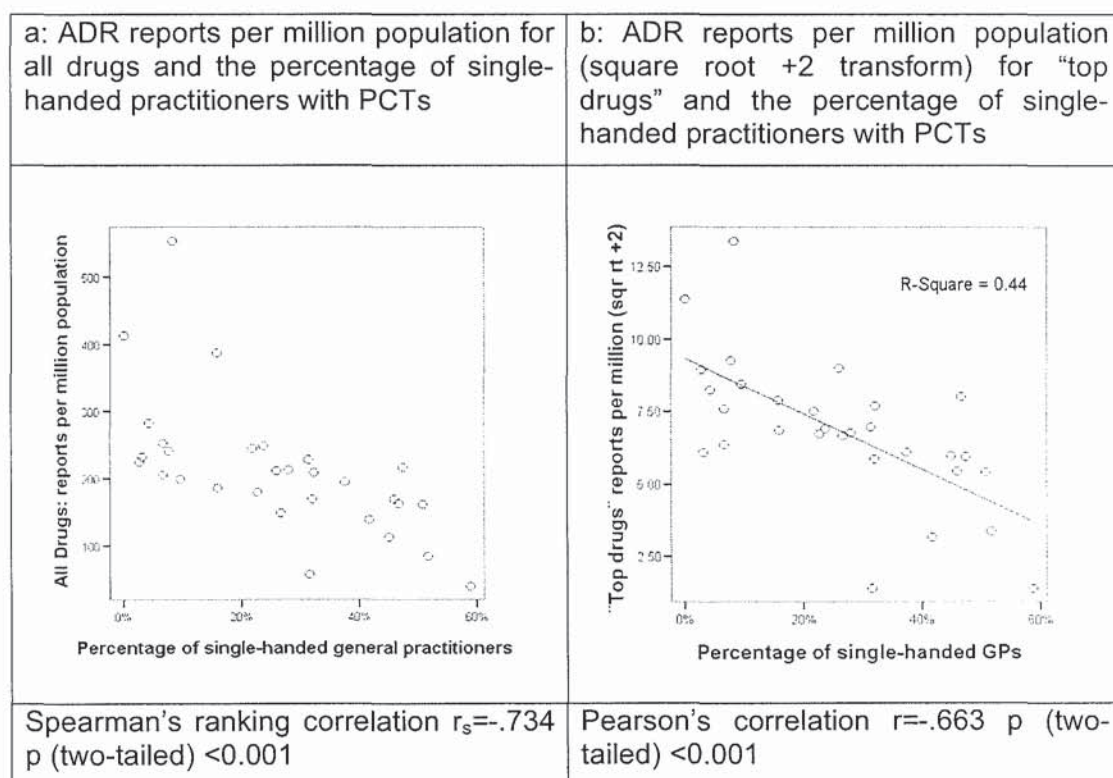
Figure 5-26: ADR reports per million population against percentage of male general practitioners with PCTs



Reporting of all drugs per million population was significantly correlated with the percentage of single-handed general practitioners within a PCT (Figure 5-27a).

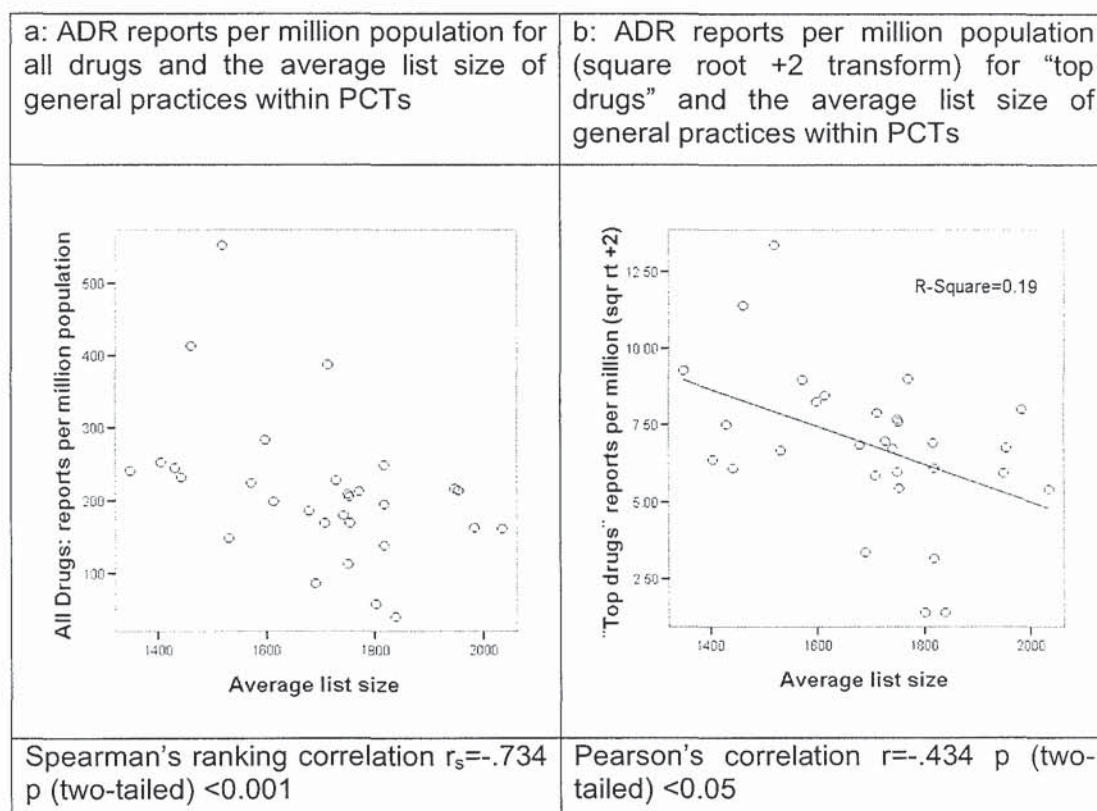
“Top drugs” adverse drug reaction reports per million population (Square root + 2 transformation) was significantly negatively correlated with the percentage of single-handed general practitioners within a PCT, (Figure 5-27b).

Figure 5-27 : ADR reports versus percentage of single-handed general practitioners in West Midlands PCTs



Reporting of all drugs per million population was significantly negatively correlated with average list size of a general practitioner within a PCT (Figure 5-28a). Reporting of “Top Ten” drugs per million population (Square root + 2 transformation) was significantly negatively correlated with average list size of a general practitioner within a PCT (Figure 5-28b).

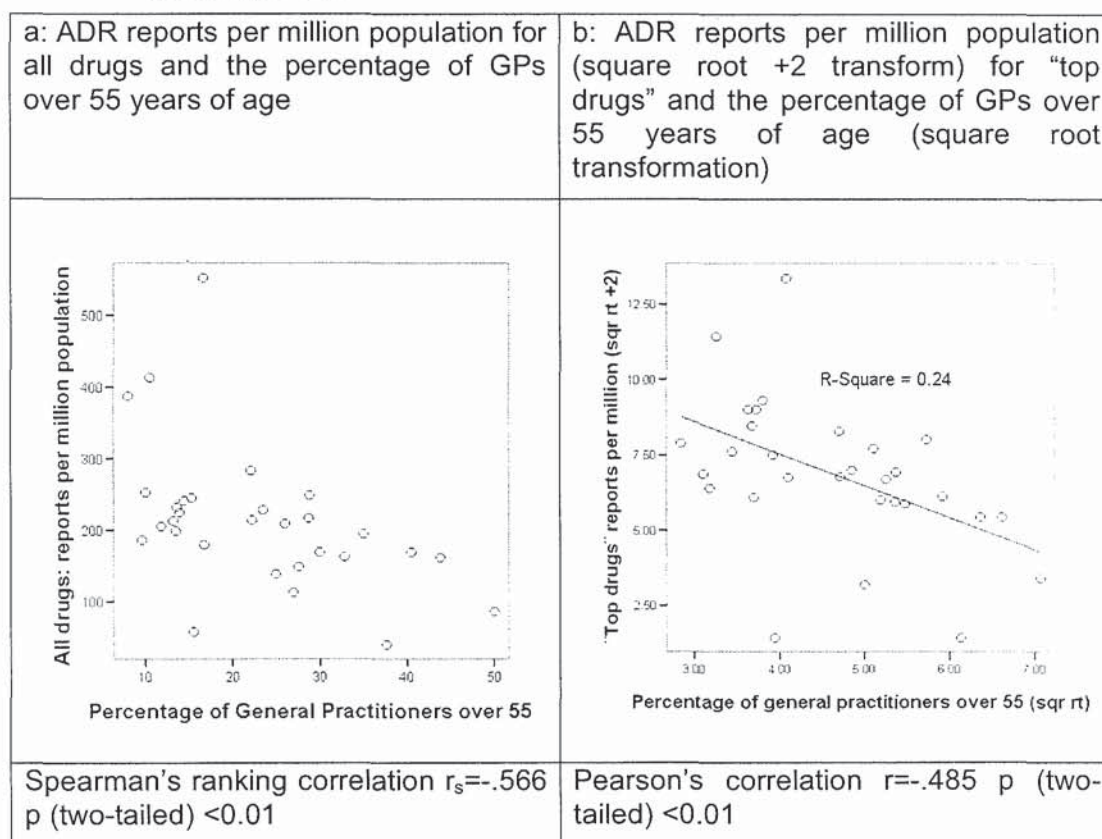
Figure 5-28 : ADR reports versus average list size of GP practice within West Midlands PCTs



The proportion of single-handed GPs was significantly associated with increases in list size (Pearson correlation $r = 0.726$ p (two-tailed) <0.001).

Reporting of all drugs per million population was significantly correlated with the percentage of general practitioners over 55 years of age (Figure 5-29a). Reporting of “Top Ten” drugs per million population (Square root + 2 transformation) was significantly negatively correlated the percentage of general practitioners over the age of 55 years old (Square root transformation) (Figure 5-29b).

Figure 5-29 : ADR reports versus percentage of general practitioners over 55 in West Midlands PCTs

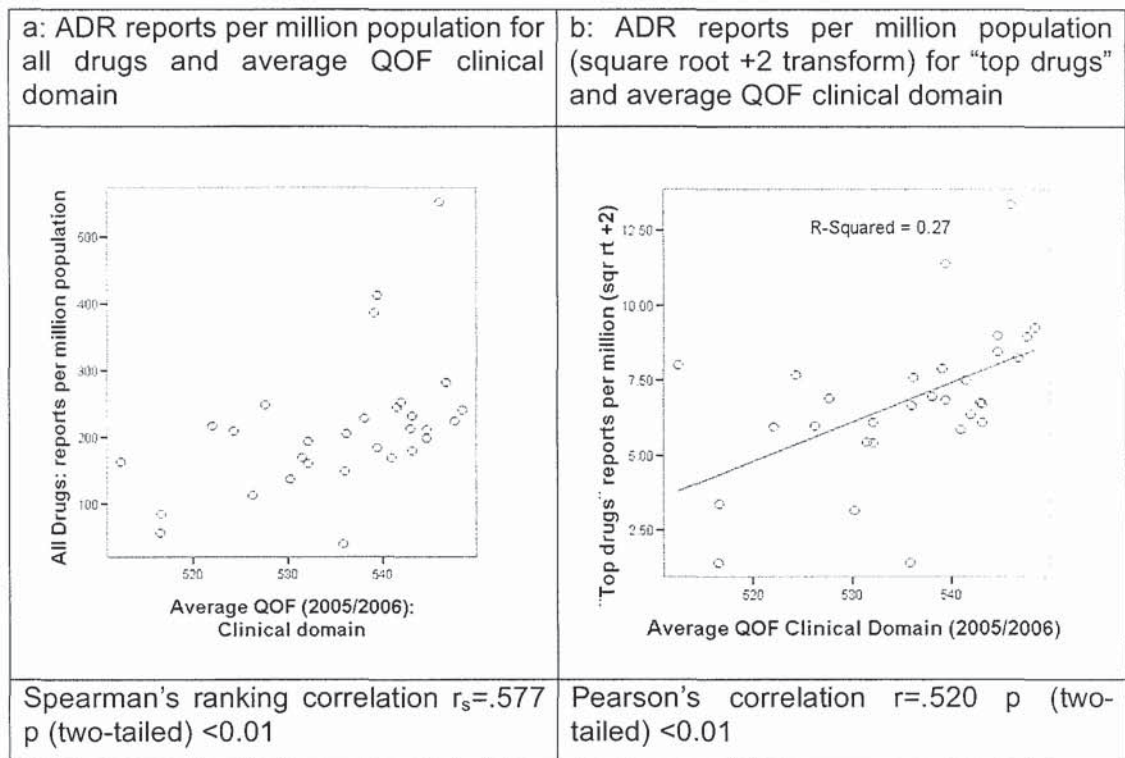


5.3.7. QOF data and Yellow Card reporting

The mean GP QOF clinical domain points per PCT in the West Midlands region was 535 (median 539), with a range of 512 to 548.

ADR reporting of all drugs per million population was significantly correlated with average QOF clinical domain points (Figure 5-30). ADR reporting of "Top Ten" drugs per million population (Square root + 2 transformation) was significantly correlated with average number of QOF points achieved in clinical domain by general practitioners within a PCT (Figure 5-30b).

Figure 5-30 : ADR reports per million population versus average QOF clinical domain in West Midlands PCTs 2005/2006

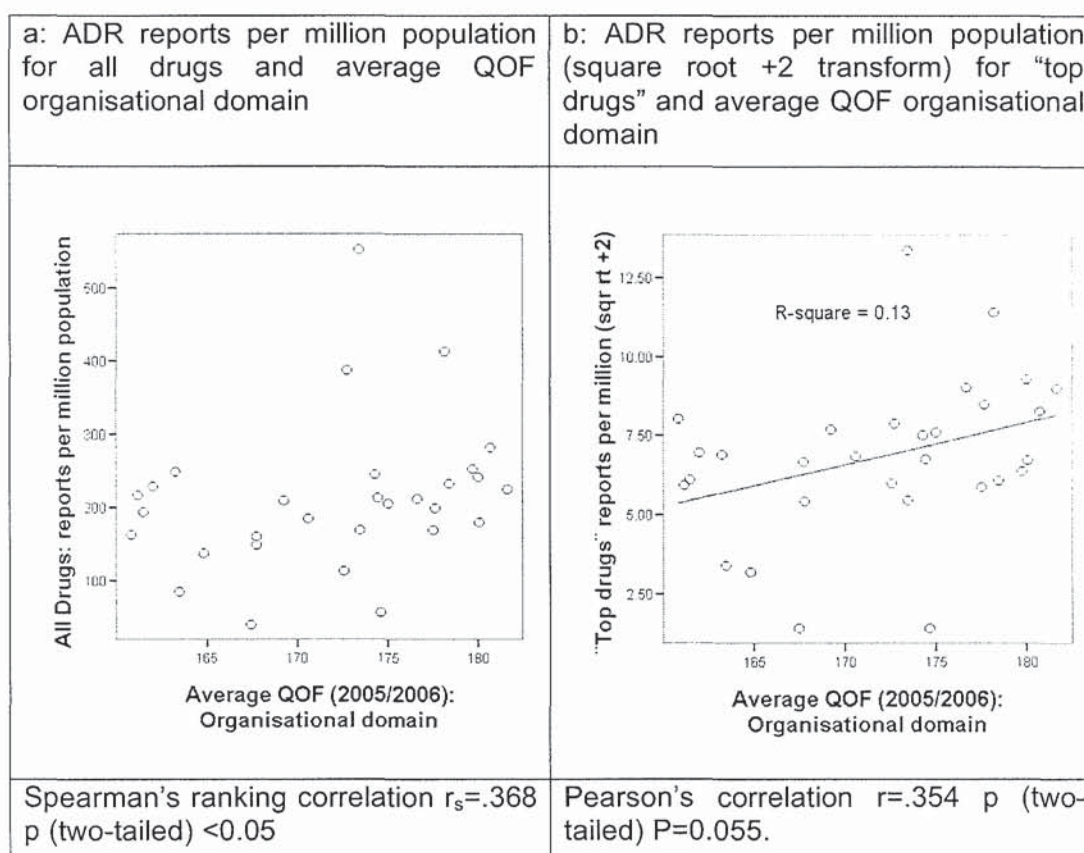


The average QOF points was significantly negatively correlated with the raised proportions of single-handed GPs, Pearson's correlation $r = -0.758$ p (two-tailed) < 0.001.

The mean GP QOF organisational domain points per PCT in the West Midlands region was 172 (median 173), with a range of 161 to 182.

Reporting of all drugs per million population was significantly correlated with average QOF organisational domain points, (Figure 5-31a). Reporting of "Top Ten" drugs per million population (Square root + 2 transformation) was not significantly correlated with Average QOF points awarded in the organisational domain (Figure 5-31b),

Figure 5-31: ADR reports per million population versus average QOF organisational domain in West Midlands PCTs 2005/2006



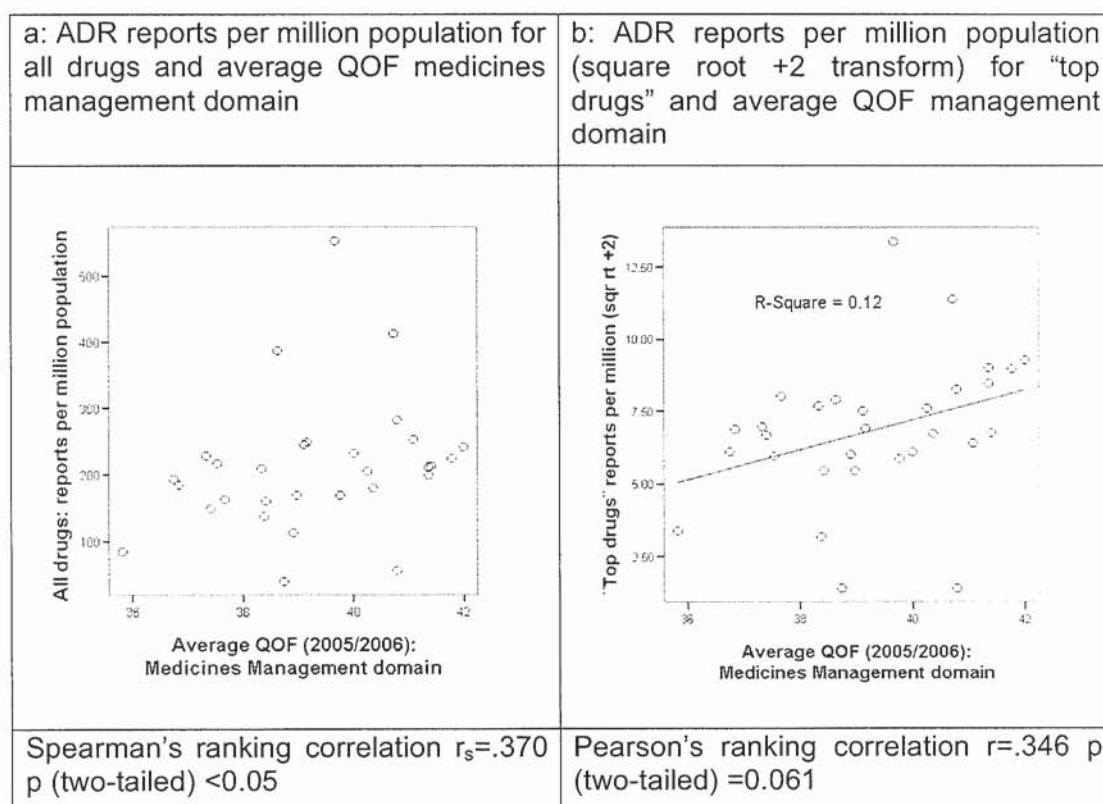
The mean general practitioner QOF medicines management points per PCT in the West Midlands region was 39.3 (median 39), with a range of 35.8 to 42.

Reporting of all drugs per million population was significantly correlated with average QOF medicines management points, Spearman's ranking correlation $r_s = .370$ p (two-tailed) < 0.05 (

Figure 5-32a).

Reporting of “top drugs” drugs per million population (Square root + 2 transformation) was not significantly correlated with average QOF medicine management points, Pearson's ranking correlation $r = .346$ p (two-tailed) $= 0.061$ (**Figure 5-32b).**

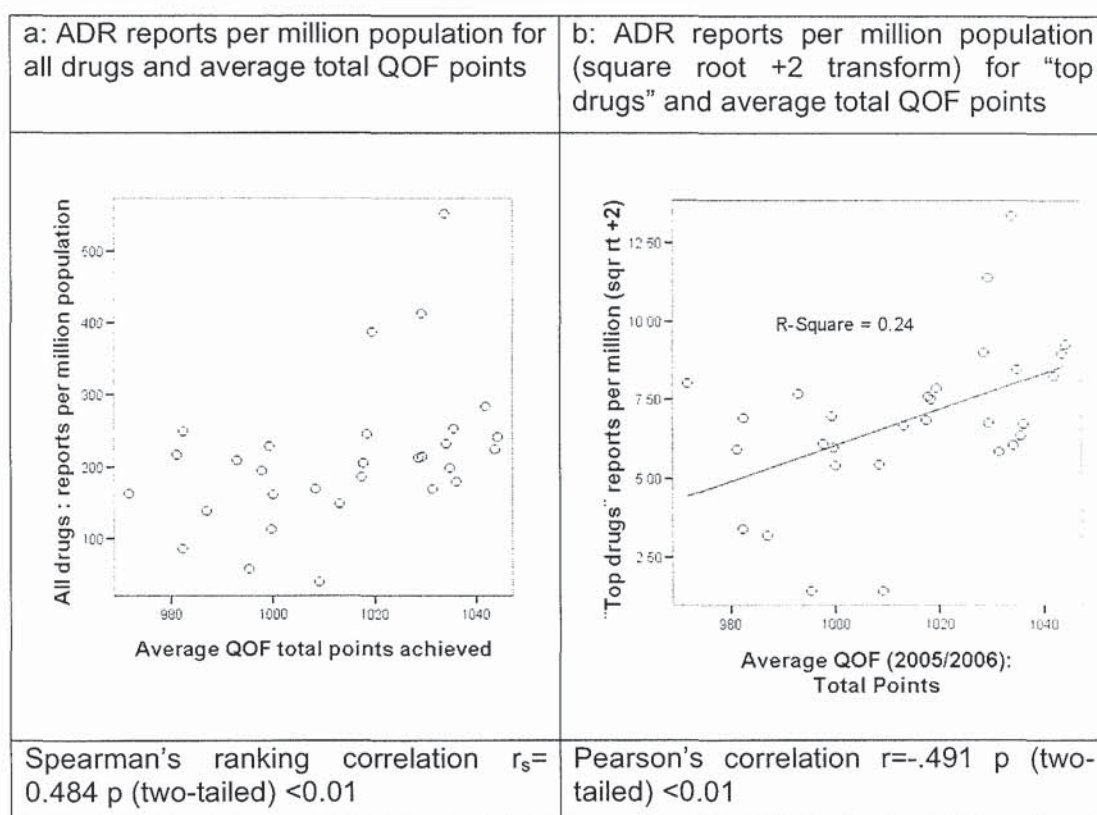
Figure 5-32: ADR reports per million population versus average QOF medicines management (2005/2006)



The mean total QOF points achieved by GPs in the West Midlands was 1013 (median 1018), with a range of 972 to 1044.

Reporting of all drugs per million population was significantly correlated with average QOF total points (**Figure 5-33a**). Reporting of "Top Ten" drugs per million population (Square root + 2 transformation) was significantly correlated with the average of the Total QOF score achieved by general practitioners within PCTs (**Figure 5-33b**).

Figure 5-33 : ADR reports per million population versus average total QOF per PCT (2005/2006)



5.3.8. Deprivation scores

There was a statistically significant negative correlation between overall deprivation scores and reporting rate per million population for all drugs, Spearman's ranking correlation $r_s = -0.55$ p (two-tailed) <0.01. This was also apparent for the reporting rate per million for “top drugs”, Spearman's ranking correlation $r_s = -0.57$ p (two-tailed) <0.01.

A similar relationship was seen between the health component of the deprivation index for both all drugs ($r_s = -0.54$ p (two-tailed) <0.01) and “top drugs” ($r_s = -0.60$ p (two-tailed) <0.001).

Higher deprivation scores were not statistically associated with increased list size, Pearson's correlation $r = 0.4$ p (two-tailed) 0.07.

Higher deprivation scores were strongly positively correlated with increases in the proportion of the single-handed GPs, Pearson's correlation $r=0.708$ p (two-tailed) <0.001 .

5.3.9. Proportion of population over 65 years of age

No statistically significant correlation was found between the number of reports per million population for both all drugs ($r_s=0.147$ p (two-tailed) 0.438) and "top drugs" ($r_s=0.128$ p (two-tailed) 0.502) and the proportion of the PCT population over 65 year-of-age.

5.4. Discussion

5.4.1. West Midlands reporting trends

The reporting of ADRs within the West Midlands as a whole has been sustained above 1000 reports per year over an 11-year period, apart from 2002. This occurred following the meningitis C reporting campaign, and may reflect some reporter fatigue due to the increased level of reporting during that period. Addition of bypass reports centrally collected from the MHRA did not change the general trends in reporting, and the 2002 dip was maintained, enabling further analysis of the West Midlands data to be undertaken, on the assumption that they were a reasonable representation of ADR reporting within the West Midlands region.

While the overall reporting rate was sustained, the professional origin of the reports shows remarkable change. Most noticeably, ADR reports from GPs underwent a dramatic fall in 2002, which continued until 2005, amounting to a total 58% fall in ADR reports from GPs over 11 years. The maintenance of the ADR reporting rate within the region was largely met by increasing numbers of ADR reports from other professional groups from 2003 onwards.

In contrast to GP ADR reporting, hospital doctor ADR reporting has been maintained. The reason for this difference is not immediately apparent. However, it may be that changes in the working environment within general practice may account for the fall. However, the fall precedes the introduction of the new GP contract on the 1st of April 2004.

Hospital pharmacists' rates of ADR reporting have continued to rise in the region, and do not appear to have affected hospital doctors reporting rates. It may be that hospital pharmacists' ADR reporting draws attention to the Yellow Card scheme, rather leading doctors to leave ADR reporting to others.

Community pharmacist ADR reporting remains disappointingly low in the region. After community pharmacists were formally accepted into the Yellow Card scheme in 1999, ADR reporting rates rose after a dip at the end of the trial period. However, within the West Midlands, community pharmacy has yet to perform as expected. Community and hospital nurse ADR reporting rates are already higher than community pharmacist ADR reporting, despite less time within the Yellow Card scheme. Expectations in the early 1990s of community pharmacist activity in ADR reporting were high, and early trials were encouraging²⁶¹. However, in 2002 the CSM noted that community pharmacy had not been as prolific as hospital pharmacy at ADR reporting²⁵⁸, especially considering the 22,000 community pharmacists in practice at the time. The difference was explained as being due to longer involvement of hospital pharmacists in the Yellow Card scheme. However, the present study still indicates no major increase in community pharmacist ADR reporting since their admittance into the scheme.

The nature of ADRs reported in the West Midlands is also changing, with a gradual trend towards an increased proportion of serious reactions being reported – apart from in 2000, when a large number of non-serious reports to meningitis reduced the proportion of serious reports. Although the proportion of serious reports can be affected by the types of drugs on the market, and bias in their reporting, it is likely that the change in the percentage of serious reports is affected by the professional composition of the reporters. The decline in GP ADR reports and replacement by reports from hospital doctors and hospital pharmacists could

explain this rise. Both of these professional groups' reports contain a high proportion of serious ADRs in comparison to GP reports.

However, even as GP reports have been falling, their proportion of serious reports has risen, possibly indicating a willingness to still report serious reactions over trivial reactions when pressures on reporting rise.

The proportion of reports related to black triangle drugs in the region, was disrupted in 2000 by the increased vigilance during the meningitis C vaccine campaign, as well as a number of reports related to bupropion which was launched in June of 2000. Nearly a third of reports in the region relate to a black triangle drug. The effect of the change in professional origin of reports is less pronounced than that seen in the proportion of serious reports. However, it should be noted that hospital pharmacists continue to report a low proportion of black triangle drugs. This may arise from a professional interest in serious preventable ADRs to well-established drugs or a bias to more easily detectable ADRs, as has been suggested previously²⁵⁵. Hospital nurses report a higher proportion of black triangle drugs than both hospital doctors and hospital pharmacists, possibly because nurse reporting may be being driven by a number of specialist nurses in particular therapeutic areas such as rheumatology. Community nurses are currently reporting the highest proportion of black triangle reports. Community nurse reporting is likely to have been influenced by the change over from the Glaxo strain of BCG vaccine used since the early 1960s to the Danish Statens Serum Institute (SSI) strain in August of 2002. This was a black triangle drug, and it was noted that reports were increased to this in *Current Problems in Pharmacovigilance*³⁶².

The overall picture of the region is that reports overall are being sustained, but that the nature of the database is changing, with an increasing proportion of reports being sourced from hospitals rather than primary care, and an increasing proportion of serious ADRs being

reported. The proportion of reports being received from doctors is also falling, primarily due to large and sustained falls in GP reporting.

5.4.2. National reporting trends

The West Midlands trend in reporting is similar to that seen at a national level from 1996 to 2006, including the dip in reporting in 2002, and the increase in reporting in 2000 due to bupropion and meningitis C vaccine reports. Reporting appears to be at a steady 13,000 Yellow Cards per year from 2004 to 2006. However, the overall national figures hide an important trend in reporting.

In years 2005 and 2006 national figures on ADR reporting have included patient ADR reports. The removal of patient reports shows a disturbing fall in healthcare professional reporting, particularly in 2006 when 22.6% of reports were lost. Nationally the large fall in GP reports has not been replaced with increasing number of reports from other professional groups, but by the input of the patient ADR reports. In the past, concerns about patient reports have been an objection to their acceptance by regulatory bodies¹⁵⁹. Now the MHRA, in the face of large falls in healthcare professional reporting, are potentially becoming dependent on patient reports to sustain reporting rates. To put the fall in healthcare professional reports into perspective, a total of 9593 reports were submitted by healthcare professionals in 2006, a level of reporting similar to that seen in the early 1980s before the withdrawal of benoxaprofen. During the 1990s the level of reporting was approximately 18,000 reports per year, virtually all from hospital doctors and GPs. In 2006, the Yellow Card scheme received 5382 from those two groups, vividly demonstrating a massive level of professional disengagement from the Yellow Card scheme.

There are some differences in the professional origins of reports nationally compared to the West Midlands region. In contrast to the West Midlands, where hospital pharmacist reporting is increasing, and other professional groups are at the least sustaining their reporting rates, all

professional groups appear to be gradually declining. Although this decline is proportionately smaller than that seen with GP reporting, this difference means that GP reports are not being replaced by reports from other professional groups. These differences may be explained by the presence of the West Midlands YCC. The centre is based within a pharmacy department in a large teaching hospital, which is responsible for half of the hospital reports within the West Midlands region.

It is important to note that this data does not include ADR reports submitted by healthcare professionals to the pharmaceutical industry. Examination of reports made to the pharmaceutical industry appears to show a gradual increase in the reporting rate, in contrast to the declining rate of direct reporting to the Yellow Card scheme. In 1996, nearly half of ADR reports were made directly to the Yellow Card scheme, by 2006 the proportion of healthcare professional ADR reports being made directly to the Yellow Card scheme had fallen to less than 30%. The fact that the Yellow Card scheme received a high proportion of reports directly healthcare professionals, rather than through the pharmaceutical industry, has been considered a strength of the scheme. The majority of reports submitted to the FDA come via pharmaceutical companies. The FDA have expressed concern about late or non-reporting of ADRs in the past, and in some cases have had to issue warnings to companies and on occasion conduct prosecutions¹⁶³. They have expressed a preference for healthcare professionals to report directly to the FDA, rather than via companies.

The West Midlands region outperformed the national reporting rate when adjusted for population, apart from 2002. However, in 2002 a large prospective study of drug-induced hospital admissions⁷⁷ resulted in an additional 1135 reports to Merseyside YCC³⁶³. Removal of these reports from the national figures made the West Midlands reporting rate per million population higher than the national reporting rate in 2002. In 2001, Bracchi et al's

intervention study²⁸⁸ led to a 135% increase in GP reporting (an 941 additional Yellow Cards) which also affected the national reporting rate.

Assuming that the performance of the West Midlands YCC is no worse or better than other regional YCCs, the removal of other YCC reports (and associated populations) from the national reporting rate is likely to make the West Midlands YCC performance stronger. As already discussed the West Midlands also had increasing numbers of ADR reports from hospital reporters, against the national trend for declining reports.

The 2004 Independent Review of the Yellow Card scheme was highly supportive of the regional centres' educational and promotional role¹⁵⁶. These results confirm the value of a regional YCC centre in stimulating ADR reporting.

5.4.3. Analysis of HES ICD10 codes

Analysis of HES ICD10 codes associated with ADRs from 1998 to 2006 in the present study did not show a clear trend in the number of ADRs. Furthermore, the present study found a clear increase in secondary ICD10 codes related to drug, medicaments and biological substances (a 55% increase over 8 years). Using HES data to examine longitudinal trends is difficult, and it may be that such year on year rises are in part caused by improvements in the application of secondary ICD10 codes to cases that were previously un-coded.

ICD10 codes themselves grossly underestimate the number of ADRs in the population, with 0.35% of hospital admissions coded as drug-induced³⁰³. This is a much lower figure than the 5% rate found in rigorous prospective studies⁷⁷.

HES data analysis has been used to examine under-reporting of ADRs to the Yellow Card scheme on three occasions^{138,140,364}, and each study has shown that HES coding does not match Yellow Card reports. However, the present study demonstrates no fall in ICD10

coding in recent years, giving some possible indication that any fall in Yellow Card reporting is unlikely to be due to falls in the numbers of detectable ADRs.

5.4.4. Hospital reporting 2004-2006

ADR reporting rates per 100,000 admissions varied widely between the acute NHS trusts in the West Midlands region, and did not appear related to hospital activity. Variation in hospital ADR reporting rates has been demonstrated previously²⁸¹. It is likely that the highest performing trust (excluding the trust where the West Midlands YCC is based) may have performed well because of its close links with a clinical pharmacology department at a local medical school and because of closer contact with staff involved at the West Midlands YCC. The reasons for differences between other trusts remain unclear. The proportion of black triangle ADR reports also varied at each hospital site, which could have been related to the proportions of the professional groups reporting at each site. High hospital pharmacist activity did match with lower proportions of black triangle reports.

Although hospital doctors still submit the majority of reports from the hospital sector, 1 in 3 Yellow Cards now comes from hospital pharmacists. Hospital nurse reporting is also an important source of reports, especially as the data suggests they report a higher percentage of black triangle drugs than other groups in the hospital sector.

There is considerable heterogeneity in the proportions of the professional groups at different hospitals. Three hospitals had no reporting from hospital pharmacists, while pharmacists made up the highest reporting group in two others. Nurse reporting did not occur in three trusts, while in one trust they were responsible for 40% of Yellow Cards. It is not known what factors lead to these differences, although training and knowledge of the Yellow Card scheme is likely to be a factor, as well as professional leadership within the hospital trusts. However, knowledge of areas of under activity with regard to Yellow Card reporting, could

be used by the West Midlands YCC to target professional groups who are under performing with specific educational programmes.

There were hospital pharmacists and hospitals doctors who had disproportionate effects on reporting rates. High reporters to the Yellow Card scheme have been identified in a previous examination of Yellow Card demographics²³². These individuals do act as exemplars of how ADR reporting can be brought into professional practice. However, the extent of this skew within hospital reporting is of concern, with nine individual pharmacists (8.5% of all pharmacist reporters) being responsible for 61% of all hospital pharmacists reporting. During the two-year period the majority of pharmacists and doctors involved in the scheme reported between 1 and 5 Yellow Cards. This could indicate an underlying failure to bring ADR reporting into mainstream clinical practice for pharmacists, and does make hospital pharmacist reporting rates at risk if certain individuals cease to practise.

During 2004-2006 a low proportion of reports from hospitals were related to black triangle drugs (19%). The top ten reported drugs without black triangle status were aspirin, warfarin, atenolol, bendrofluazide, furosemide, ibuprofen, celecoxib, ramipril, simvastatin and paroxetine. These, apart from simvastatin, do tally with the drugs found to be causing ADRs in 2004 UK prospective study in the UK⁷⁷.

Five of the top ten black triangle drugs reported to the West Midlands YCC were drugs used in rheumatology. The West Midlands YCC has made professional contact with the specialist nurses within this area in recent years, which may account for the prominence of these drugs.

It was hypothesised that markers of increased pharmacy involvement or performance in medicines management might be correlated with ADR reporting rates. However, no significant correlations between Healthcare Commission medicines management performance criteria performance and ADR reporting rates were seen. It may be that such

indicators are too blunt an instrument to give an indication of wider clinical performance, or subject to gaming.

Spoonful of Sugar, which was the basis for the current medicines management programme in the NHS, made reference to ADRs³²⁷. However, current medicines management criteria are focused on medicines management issues that directly affect the patients within the care of acute NHS trusts. Yellow Card reporting serves a public health role to the whole of the NHS. A medicine management criterion for ADR reporting in acute NHS trusts could perhaps increase management and professional focus on ADR reporting. As Chapter 3 notes, ADR reporting is seen with decreasing importance by higher management. ADR reporting can also signify clinical engagement with patients by hospital staff and should be seen as a clinical governance issue.

There is therefore an opportunity for the MHRA to work with the Healthcare Commission to establish mechanisms of feeding back ADR reporting rates to NHS trusts. Although the Yellow Card scheme was founded with a key principle that Yellow Cards would not be used as a mechanism for auditing doctor performance, there would appear to be no reason why broad figures relating to hospital performance would violate that principle. Using aggregated Yellow Card data in an anonymized way to measure the performance of institutions would not identify individual reporters.

5.4.5. Primary Care ADR reporting 2004 to 2006.

The first finding of the analysis of PCT Yellow Card reporting during 2004-2006, was that considerable variation in Yellow Card reporting rates per million population existed (range 58 to 552 reports per million population). This reporting rate was not related to the population of the PCT, with the highest reporting PCT having the second smallest population. The majority of reports from primary care were from GPs (70%), with variation between the proportions of Yellow Cards from each profession.

In contrast to Yellow Card reports from acute NHS Trusts, Yellow Card reports from PCTs were more concerned with black triangle drugs, reflecting the known tendency of GPs to report black triangle drugs¹³⁷. The top ten drugs for 2004-2005 and 2005-2006 both contained 9 black triangle drugs, with the well-established simvastatin appearing in both lists. The combined list of 14 drugs accounted for 30% of all reports from primary care. In a study in Scotland looking at top ten drugs in years 2000 and 2001, it was found that the top 14 drugs were responsible for 62% of reports²⁸³. In the present study, 14 “top drugs” were responsible for 3.3% of all prescribing, but 30% of all ADR reports. As thirteen of these drugs were black triangle, this demonstrates that Yellow Card reporting is biased towards newly marketed agents.

5.4.6. Primary care correlations.

Both “top drug” reporting and “all drugs” reporting were strongly correlated with PCT populations, which justified the decision to adjust reporting rates of PCT population size for further analysis. The rate per million population for all drugs could not be transformed into a parametric dataset, so Spearman’s ranking correlations had to be performed for all further analysis. However, the “top drugs” Yellow Cards reports per million was successfully converted in parametric data.

There was a significant negative correlation between the prescribing of all drugs and “top drugs” per thousand population, and the reports per million population. The r^2 value for “top drugs” was 0.18, showing that 18% of the variation in the Yellow Card reporting rate for “top drugs” could be explained by variation in the prescribing rate. This indicates that PCTs with higher prescribing GPs are less likely to report ADRs to “top drugs”, 13 out of 14 of which were black triangle drugs. This may indicate that those doctors who are more likely to take up the use of black triangle drugs, are less likely to use the Yellow Card scheme. The implication of this is that those who are therapeutically conservative are more likely to use

the Yellow Card scheme, but correspondingly less likely to be prescribing the drugs that reporting is particularly valuable for. However, the fact that all prescribing was also negatively correlated with Yellow Card reporting rates, may mean that more heavy prescribing in general is associated with lack of interest in pharmacovigilance, as expressed by use of the Yellow Card scheme.

The Scottish YCC also examined reporting within their centre²⁸³. There were some important differences between their study and the present one. They examined all Yellow Card reports, including those from acute NHS trusts, although prescribing data was from primary care, not hospital prescribing. They also had a smaller number of health boards compared to number of PCTs with larger variation in population size (range 26,450 to 2,210,390) compared to that in West Midlands PCTs. When they examined the correlation between Yellow Card reports to CSM Scotland per million population and the number of primary care prescriptions per 1000 population (top ten medications, 2 years combined) they found significant positive correlation $r = 0.66$, $p=0.04$. This means 44% of the observed variation in reporting rate was attributed to variations in prescribing rate within the same population. When they excluded the largest health board, this correlation increased to $r=0.74$, $P=0.02$. They found no correlation when this was applied to all drugs. It is not clear why Clark et al found the opposite result to this study. A possible reason for the difference is that Yellow Card reporting from hospitals sited within the Scottish health boards heavily affected the reporting rates of health boards. It would be interesting to see the Scottish study repeated again after the removal of hospital reports from the analysis.

There is some supporting evidence that supports the present study's suggestion that higher prescribers are poorer reporters. Inman and Pearce examined 28,402 general practitioners in the UK identified through PEM studies, calculating their return rates for post-marketing drug safety information requests from the DSRU's green card scheme²⁸². The return rate can be

considered an indicator of the doctor's interest in drug safety and is analogous to completing a Yellow Card. Doctors were divided into six groups based on relative levels of prescribing of drugs prescribed. The major finding of the study was that the 10% of doctors who prescribed drugs most heavily were responsible for 44% of total prescribing of new drugs after the first six months of their introduction, with a consistent inverse relationship between the number of prescriptions and the response rate to PEM studies. Interestingly, as the prescribing rate went up the proportion of women decreased (from 46% to 9%), and the number of overseas qualified doctors rose (13% to 47%).

The finding from this study of a negative correlation between the number of reports per million population and the number of prescriptions per thousand population for both the "top ten" reporting drugs and "all drugs" would appear to provide a similar message. Those that prescribe drugs more heavily are less likely to report the adverse effects of the drugs concerned. Whether this is because of a lack of awareness of the harm caused by prescribed medicines or general positive view of the pharmaceutical industry is not known.

A study by Florentinus et al³⁶⁵ examined the dispensing data of 103 Dutch GPs, selecting five new drugs as study cases: salmeterol/fluticasone, rofecoxib, esomeprazole, tiotropium, and rosuvastatin. All five of these drugs had rapidly achieved marketed penetration and were in the fastest growing expenditures within one year of marketing in Holland. A minority of GPs were responsible for 50% of prescribing of each drug, for example 10.9% of GPs were responsible for prescribing 50% of rofecoxib prescriptions. A positive attitude towards new drugs was positively associated with the prescribing of new drugs (OR=1.65; 95% CI 1.26-2.15). GPs who were more industry orientated were also more likely to prescribe new drugs (OR=1.37; 95% CI 1.17-1.61) compared to those less interested in pharmaceutical industry relationships.

The present study found that the reporting rate per million population for all drugs and “top drugs” was negatively correlated with the proportion of male GPs, the proportion of single-handed GPs, the average list size, and the percentage of GPs over 55 years-of-age. The finding that an increasing proportion of female GPs was associated with higher levels of reporting may be based on gender differences in the introduction of new therapies and differing views on risk management of medication³⁶⁵. It is not clear why PCTs with higher proportions of older GPs were poorer reporting areas, although it may have been related to differing levels of training.

The proportion of single-handed GPs was a particularly strong correlation, with 44% of the variation in reporting for “top drugs” being explained by this attribute of PCTs. When prescribing by single-handed GPs has been examined, the data is inconsistent^{366,367}, with arguments that group practices can be more heavy prescribers. However, Florentinus found single-handed GPs were heavier prescribers (OR=2.55; 95% CI 1.70-3.83)³⁶⁵.

Data in the present study is not at the GP level, but the association of higher prescribing leading to lower reporting rates with PCTs is interesting in the context of Florentinus et al’s results. It may be that those high prescribing GPs who are more easily influenced by the pharmaceutical industry are not reporters.

There was no correlation between the proportions of the population of a PCT over 65 years of age, and the ADR reporting rate for “all drugs” and “top drugs”. However, it should be remembered that this was a crude patient characteristic based on the general population data, rather than the characteristics of the individuals prescribed medicines.

However deprivation scores were negatively correlated with ADR reporting rates for “all drugs” and “top drugs”. Deprived areas were strongly correlated with increases in the

proportion of single-handed GPs. It is possible that struggling inner city health services, with a diverse population, find ADR reporting more of a challenge.

The present study found that average QOF performance of PCTs was significantly correlated with increased Yellow Card reporting. It has been suggested use of a quality indicator in the GP contract could be used as a “carrot” to increase Yellow Card reporting rates²⁸⁹. However, if the present study is correct, then it would appear that GP practices who do perform well in the contract, are also the ones more likely to report. Whether the introduction of a QOF target would raise Yellow Card reporting rates higher is open to question. Setting of a Yellow Card target would also mean that those who did not perform would be being punished by not meeting a target, by loss of earnings. Attributing negative consequences to the Yellow Card scheme in this way may change the perception GPs have of the Yellow Card scheme, and does go against the spirit of the original aims of the scheme that stated that all reports would be in confidence. The supply of an individual GP’s reporting performance statistics to a contractual department of the NHS, could be seen as breaking that confidence. In addition, bringing the Yellow Card scheme into the NHS political arena and tying it to contractual matters (which are subject to short-term political change) could damage the long-term viability of the scheme if the reporting culture was changed to a financially driven target. Future changes in the GP contract under different governments, or even increased private provision, could see the Yellow Card scheme returning to voluntary non-fee driven reporting with unpredictable consequences.

5.4.7. Conclusion

Overall ADR reporting rates from healthcare professionals are undergoing a major decline, to a rate not seen since the early 1980s. In particular, the number of GP reports to the Yellow Card scheme has undergone a large decrease. Reporting from the hospital sector is encouraging, with hospital doctor reporting and pharmacist reporting appearing to

compliment each other. Primary care is more disappointing with the shortfall in GP reporting not being taken up by community pharmacists. The reasons for community pharmacists' failure to engage with the Yellow Card scheme, following successful trials, are not known.

However, patient reporting has become important in a short two-year period. It is likely that focus on patient reporting will continue in future years, and paradoxically, reports that were once not valued by the MHRA will be seen as a way of maintaining reporting rates.

The variation in PCT and acute hospital reporting rates is of interest to organisations like regional YCCs, who can use such data to target low reporting areas or hospitals with educational visits. In addition, such information may be useful to provide feedback in order to stimulate reporting, or used by third parties (such as the Healthcare Commission) as medicine management criteria, particularly in acute NHS Trusts where current medicines management criteria do not currently correlate with ADR reporting rates.

Some characteristics of PCTs, such as the proportion of single-handed GPs, the proportion of male GPs and the proportion of GPs over 55, were negatively correlated with ADR reporting. However, this is relatively crude data, and examination of individual GP type and Yellow Card reporting would give a more accurate picture.

The finding that higher prescribing areas were less likely to have high reporting rates, is interesting, since it may suggest that doctors more interested in clinical pharmacology may be more likely to report, or perhaps that high reporters to the Yellow Card scheme are therapeutically cautious individuals.

Chapter 6 General practitioner reporting: A qualitative case study

6.1. Recruitment

The study recruited 27 GPs. The numbers of each type of GP invited, successfully recruited, and finally interviewed are noted in Table 6-1.

Table 6-1 : Recruitment of GPs to Qualitative Case Study

Reporter Type	Invited	Agreed	Interviewed
Regular reporters	46	15 (33%)	10
Lapsed reporters	21	11 (52%)	10
Non reporters	100	3 via letter (3%) 5 by convenience sample	7

Regular reporters were sent recruitment letters during the month of March 2006, lapsed reporters during the month of April 2006, and non-reporters in two batches during August 2006 and November 2006. Interview dates overlapped for all three groups, due to difficulties in arranging interviews. Interviews took place between April 2006 and March 2007.

Non-reporters were the last group to be contacted. A poor response rate to the letter led to alternative sources of non-reporters. Three GPs were recruited via a colleague's partner who was a general practitioner, and a further two GPs via a medical education meeting. Even after acceptance to be interviewed, it was impossible to arrange meetings with some GPs due to an inability to contact them directly via a phone, and failure of the GP to respond to messages. For this reason, despite multiple attempts to contact GPs the decision was eventually made to abandon the attempt to recruit them.

Interviews were conducted in a place convenient to the GP, which, with the exception of one GP, was in their practice – in the majority of cases within the GP’s own consultation room. One GP was interviewed at a PCT headquarters – where he worked on a part-time basis.

6.2. *Analysis of interview data*

Interviews were transcribed in full and then analysed with emergent themes and coding used to inform future interviews. Free-coding in QSR N6 led to 98 codes being created. These were then organised into a tree structure of nodes in several conceptual categories. As part of the analysis memos were created in QSR N6 to further refine thinking about the coding structure.

Amalgamation of the memos and coding led to six main conceptual categories relating to ADR reporting:

- Knowledge and awareness of adverse drug reactions and the Yellow Card scheme
- The Act of Reporting.
- Personal Motivations.
- Barriers to reporting ADRs.
- Strategies for increasing reporting.
- Views on the MHRA and the pharmaceutical industry.

Throughout the following text the following codes are used are used to identify interviewees and their associated quotes:

N = Non reporter. i.e. N6 indicates non-reporter number 6

L = Lapsed reporter i.e. L3 indicates lapsed reporter number 3

R = Regular reporter i.e. R2 indicates regular reporter number 2

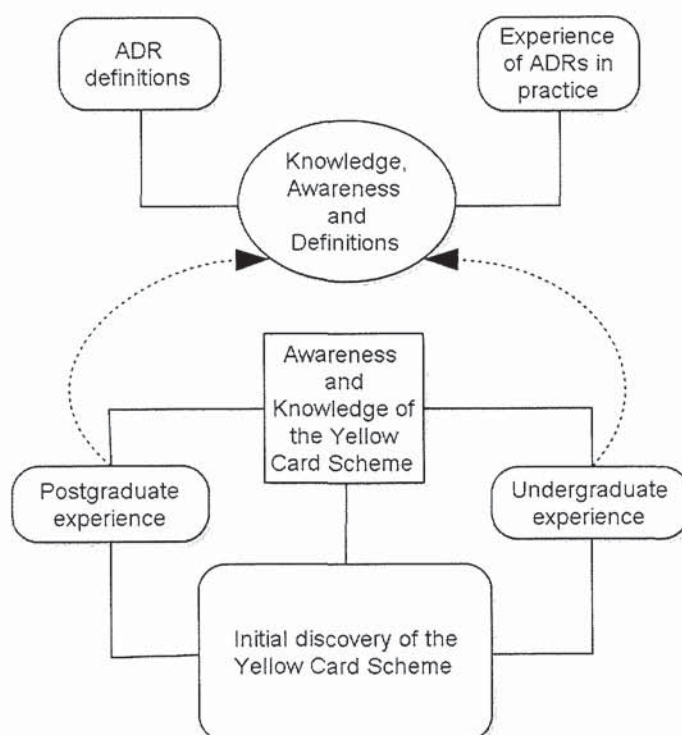
The use of the terms “regular reporter”, “lapsed reporter” and “non-reporter” refers to the categories of interviewees defined in Section 2.6.7.

The use of the term “reporters” indicates both regular and lapsed reporters to the Yellow Card scheme.

6.3. *Knowledge and awareness of ADRs and the Yellow Card scheme*

A key area of coding that evolved from the interviewees was the interviewees’ knowledge and awareness of adverse drug reactions and the Yellow Card scheme. Before even considering the filing of a report of a suspected ADR, a GP would have to be open to the possibility of an event being associated with a drug and apply terminology (such as ADR) to the event to indicate the event was associated with the drug. In addition, the GP would have to be aware of the Yellow Card scheme. Figure 6-1 shows a proposed relationship between the conceptual categories found during interviews.

Figure 6-1 : Knowledge and awareness of adverse drug reactions and the Yellow Card scheme



A reporter's initial discovery of the Yellow Card scheme raised awareness and knowledge, which postgraduate experience and undergraduate experience also contributed towards. Postgraduate and undergraduate education also contributed to more general knowledge about drug safety, such as an understanding of the likelihood of ADR occurring in practice, and the working definitions of what constitutes an ADR. Practical experience of ADRs in practice also contributed to interviewees' knowledge and appreciation of the extent of harm caused by medication.

The following discusses in more depth the issues raised by interviewees on these concepts.

6.3.1. ADR definitions

GPs held varying definitions of what constituted an ADR and exhibited differing use and understanding of terminology. Some GPs drew distinctions between side effects and ADRs, seeing them as differing categories of events. Side effects were defined as ADRs that were already known about (i.e. listed in the BNF), or an event of a less serious nature.

N6 There are side effects, I've seen a lot of coughs with ACE inhibitors recently, because I am doing a kidney disease audit and I'm starting a lot of patients on ACE inhibitors, but that is a known common side effect. I've not seen any adverse reactions as such, you know serious reactions.

L4 Somebody I started on a SSRI and I'll tend to start on half days and tell them they're going to feel nausea and queasy for the first few days and - but that's sort of the main side effect, isn't it? Rather than an adverse reaction. So I think we've got to get tighter on our definitions. Do you know what I mean?

One interviewee made reference to using the BNF to check to see if the event might be a side effect (the BNF lists ADRs as side effects), and on the basis of the presence of the reaction in the BNF would decide whether or not it was an ADR.

L9 I think I could report more, you know, when I focus on it. And then I think that perhaps it was just a side effect, not what one would truly call an adverse reaction. And I'd like to know the difference between those two things. When I was just vaguely thinking about you coming today, I thought that's the critical thing for me as a prescriber - what is the difference between side effects? And so I sort of explained what I think is the difference, if it's recognized in the BNF and at the top of the list.

But if it's more unusual and low down in the list, I think that I should report this because they may not be aware that it's happening as much as it is.

Frequently pharmacologically predictable or preventable reactions were not considered to be ADRs by interviewees. This view extended to serious adverse reactions, such a severe haemorrhage associated with the use of oral anti-coagulants.

L6 Warfarin makes you a bleeder, if you bleed then why report? It doesn't make sense to me. I'll report angioneurotic oedema to an ACE or severe liver problems with a statin, but that is different. Bradycardia with beta-blockers is not a side effect, it is an expected effect.

Reactions that are extensions of the pharmacological mechanism of the drug may not be seen as ADRs, especially if there is a failure of monitoring or an element of error in dosing. ADRs were more likely to be viewed as reactions that occurred due to the intrinsic ability of the drug to cause harm without prescriber error in relation to dosing, contra-indications, or monitoring.

I If it was a haemorrhage to warfarin?

N5 [Long pause and sigh] That's not really an adverse reaction is it. You are giving warfarin to try and extend the clotting time, so that's a slight exaggeration, it's presumably because someone had overdosed on it or somebody hasn't monitored enough.

Some interviewees would describe ADRs in terms of severe allergic reactions, discounting more minor reactions to drugs as unwanted side effects.

N5 I suppose once or twice a month, I'll see somebody with, in terms of, I saw someone this morning who was not tolerating amlodipine. They had some kind of gastro-intestinal disturbance. So they weren't prepared to continue with it, so I suppose that's the most recent adverse reaction that I have seen. That was more just an unwanted side effects as opposed to an allergic type of reaction.

The definitions a GP used to classify a reaction could influence the decision to report a reaction; for example for some interviewees side effects were considered less reportable than ADRs by those GPs that made the distinction. It is important to note however that there was

considerable heterogeneity in all terminology used by interviewees, and that definitions did not always match those in specialised literature.

6.3.2. ADRs in practice

Interviewees had varied experience of ADRs in practice. Lapsed and regular reporters comments showed a high awareness of ADRs in practice, describing them as a frequent occurrence.

L2 It depends on what you mean really, if they come and say I took those tablets and they made me feel dizzy, or gave my little boy Johnny amoxicillin on Monday and he's come out in a rash on Wednesday and do you think it is the medicine doctor? Then sure I get a lot of that.

R6 I think things like anti-hypertensives, calcium antagonists, pretty often. People get swollen legs with them and I don't report that. Maybe I should do. I think sort of minor adverse reactions I'm seeing everyday in my surgery. But they are minor things, sort of achy pains, I've started on my statin or my ankles are swollen. Or I'm getting hot flushes, or constipation from a calcium antagonist. So that sort of thing, but not big reactions.

More serious events were noted as rare and significant events. Significant suspected ADRs were cited by some regular reporters in relation to recent drug controversies, such as cardiovascular events occurring after the use of COX-II inhibitors.

A number of lapsed and regular reporters raised significant ADR anecdotes from their training and current practice, that had re-enforced their commitment to be vigilant for ADRs. These anecdotes were used as justification for continuing support of the Yellow Card scheme. Some of these anecdotes also led to feelings of guilt about harm caused by prescribed medicines (see section 6.6.3). Past experience of reactions sensitised reporters to the possibly of future ADRs.

Reporting GPs frequently cited experience of serious adverse reactions leading to hospitalisation or fatalities, although experience tended to be second hand following the discharge of a patient from hospital or death of a patient within hospital. When serious ADRs were found by the GP, they would be referred to secondary care. Some interviewees noted

that communication from hospitals about serious ADRs could be delayed, especially in the case of drug-induced deaths.

Some lapsed and regular reporters argued that the consultation process and structure of questioning patients was not designed to pick up ADRs, suggesting ADRs were easy to overlook and that a conscious effort had to be made to discover them.

R1 Because the way in which we structure our consultations, the way in which we gear our questioning is not designed to pick them up. If you are, if you set up, you must know all this better than I do, if set up a study looking at the efficacy of a drug, and you, and then you enquire as to how good the drug has been you'll get a very different set of responses from a study, as compared to a study set up to look at adverse drug reactions where you pick up all the things that happened since somebody started a particular drug.

L8 I always try to impress on our registrars, our trainees, you must consider the iatrogenic effects of something, it is very easy to overlook the drug side of things, you have got to make a conscious effort to think "is there a drug that could be causing this?" let's look at the prescribing and see what they are on. Some patients make the correlation, some patients present the symptoms and you've got to make the connection.

A regular reporter noted that his knowledge of patients over extended periods of time was important to find ADRs, and was concerned that his future move to locum duties would impair his ability to find ADRs.

Although some non-reporters did report seeing fairly regular minor ADRs, sometimes causing changes in drug therapy, there appeared less awareness of ADRs. Anecdotal reports of ADRs were less likely to be elicited when asked about recent ADRs they had seen compared to reporters. Some individuals argued they had not reported ADRs, since they had not seen any in practice or that ADRs occurred only rarely.

I Can you remember the last time you saw an adverse drug reaction?

N5 A severe adverse drug reaction or a minor one?

I Either.

N5 Well, a minor one. I was doing an out of hours session about 3 weeks ago and I saw a child who'd had a reaction to penicillin. It was a drug rash, a rash.

- I So how often do you come across minor ADRs?*
- N5 Er, are you talking about allergic reactions or side effects?*
- I Just what you would consider minor or trivial reactions.*
- N5 I suppose once or twice a month, I'll see somebody with, in terms of, I saw someone this morning who was not tolerating amlodipine. They had some kind of gastro-intestinal disturbance. So they weren't prepared to continue with it, so I suppose that's the most recent adverse reaction that I have seen. That was more just an unwanted side effects as opposed to an allergic type of reaction.*
- I In terms of the more serious adverse reactions can you remember any?*
- N5 [Pause] I actually don't think I can remember the last really serious anaphylactic type reaction, or that sort of thing. No I can't remember.*

Sometimes this view could be contradicted by the same GPs suggesting patients experience ADRs quite often.

- I When is the last time you saw an adverse reaction?*
- N4 I can't remember. A long while ago.*
- I A long time ago?*
- N4 I haven't reported any.*
- I Would you say they are quite rare?*
- N4 For my criteria, it is rare yeah, but from the patient's criteria they tend to see them quite often, I think this morning someone said their chloramphenicol was causing eye to have a sty. Which to me is illogical, but the patient believe it was, because the eye had some irritation and now they have got a lump there.*

6.3.3. Knowledge of the Yellow Card Scheme

Regular and lapsed reporters showed a good understanding of the purpose of the Yellow Card scheme. Reporters generally focused on the use of the Yellow Card scheme to uncover safety issues related to newly marketed drugs or unlabelled ADRs.

- R2 I've always had an interest in it. And when the scheme was introduced I felt that it was a valuable thing to take part in because it would build up the depth of knowledge of side effects and iatrogenic disease basically, because we still know that a high proportion of patients are actually hospitalised because of iatrogenic disease. Look at anti-inflammatory drugs and gastro intestinal bleeds and so on. So, it's still a very important area.*

L8 *Good monitoring of drugs, until they are in common use they are still at guinea pig stage despite the trials, you are still waiting for the population as a whole to be exposed to these drugs and we all know of significant drugs that have gone through all the trials and passed, and it is not until they are in common use that the problems are shown up.*

However, while reporters to the scheme could outline the general purpose of the scheme, and the mechanism of data collection, there was relatively less understanding of what happens to reports once submitted or what the value of the reports was to signal generation.

R7 *Well, I suppose they are part of a broader picture. I don't suppose that anything I send you in an individual report makes an earth shattering difference, but it just builds up the picture, I suppose if I reported some really dreadful reaction you could tie that done to a particular drug it possibly could - I don't think I've ever done that yet. It's more of just being one of hopefully quite a lot of people reporting.*

Most regular reporters were clear that the Yellow Card scheme delivered a benefit and value to drug safety, and this was cited as a reason for reporting. Value was ascribed to what the scheme delivered to the medical community, as well as that delivered to patients; some argued that no other way existed of picking up reactions occurring in general practice. Interviewees who had moved to the UK from overseas were impressed with the scheme contrasting it to the relatively lower priority drug safety had in their country of origin.

R6 *As a GP registrar, actually I'm a xxxxxxxxxxxx graduate and I worked in xxxxxxxxxxxx for three and a half years before I came to the UK. When I heard about the Yellow Card system I was amazed and delighted that there was such a well formalised system of reporting adverse drug reactions.*

Although some non-reporters indicated some understanding of the purpose of the Yellow Card scheme, these were underdeveloped in comparison to those of reporting GPs. Non-reporters had poorer understanding of the operation of the scheme and were less clear of its benefits and role in drug safety compared to reporting GPs.

N1 *I have heard of it. Yes, not that I have used it very much. And my understanding is that it's basically a way of keeping an eye on new drugs that come out, and sort of, you know, reporting any adverse effects. If there's anything serious in it and whether or not the production people or whoever produce the drugs, need to either withdraw it or whether they can continue. I assume that's the point of it.*

Sometimes lack of a direct personal benefit led to dismissal of the scheme as "not very useful", although the mere existence of the scheme was taken by some as evidence that it must be worth running.

Not all non-reporters were ignorant of the value of the scheme, although a valuing of the scheme by one non-reporter was tempered by the fact that he had submitted no reports to ADRs for several years.

Reporters to the scheme viewed collective action in drug safety as the only way to find new reactions to drugs, in order to find patterns of new ADRs.

L9 *I think it's essential. I don't see any other way that you could find out about unwanted or unusual reactions about drugs unless the people using the drugs and the patients report these things to some central place, where then that can all be looked at in a sort of collective way, and any obvious problems can be noticed. So I think it's essential.*

Well, if nobody reports things that happen, we won't know anything about drug side effects. So I do see it as an important way of finding out things that happen to people when they're on drugs. And then it's a way of drawing all that information together to see if there are adverse reactions that can be predicted, understood, or noticed for the very first time. Obviously if we didn't report - and there was one major one - then you couldn't have predicted that, where as if there were several little minor ones that might show a pattern, which is important for us all to know about.

Some reporters were aware of the numbers of reports received by the supply of feedback from the Yellow Card scheme in the form of DAPs. Although knowledge of specific withdrawals and regulatory action was not always elicited from reporters, there was a general sense in which reporters viewed the Yellow Card scheme as being involved in drug withdrawals. One interviewee made a connection between reports he had made and the withdrawal of a product.

Major pharmacovigilance events, such as thalidomide, or the more recent safety concerns about COX II inhibitors were most likely to be raised. A small number of regular reporters did raise the safety of COX II inhibitors and asked if the Yellow Card scheme detected the cardiovascular events associated with rofecoxib.

L4 *I think it's picked up a lot of, interestingly, Tell me, would it have picked up rofecoxib? Because I mean that was all a big marketing trial wasn't it when they're trying to show that it reduced colonic cancers and they suddenly find that sure it did, but everybody died in the meantime.*

One GP to note the scheme “works to a degree” and cited the withdrawal of rofecoxib as a success of the scheme. Those that were aware of specific issues of drug safety highlighted by the Yellow Card scheme cited these as a rationale for the utility of the scheme.

One regular reporter felt the value of the scheme had declined since the late 1990s, he was unable to explain why and still valued the scheme himself.

I *What is your understanding of the value of the scheme?*

R8 *The value of it? I'm not sure about that to be honest. I think it has changed over the years. That is my take on it.*

I *In what way?*

R8 *Well, and this is just a feeling a guess and not based on any thing, it used to seem to be very important, when I first started back in 1997-98, but somehow it seems to have sort of lost that, that might be just a sort of personal thing.*

6.3.4. Awareness of the scheme

Many interviewees were first made aware of the Yellow Card scheme at medical school, or when training as a junior house officer within hospital or during GP training.

R7 *Oh, I think as a medical student. Have there always been Yellow Cards in the back of the BNF? I'm not sure. In my first medical job the BNF was one of the most useful things you had to carry around with you and right from then I've been aware of the Yellow Cards in the back.*

Others had come across the scheme during GP training.

I *Can you remember when you first became aware of the Yellow Card scheme?*

R8 *I'm sorry I don't remember, it may have been when I was a junior hospital doctor, but it was certainly being talked about when I was with my first GP trainer. When I was a registrar, because we did talk about prescribing as one of the first tutorials we did.*

Even some non-reporters were able to cite specific undergraduate training or experience of completing a card while a junior doctor.

N2 Gosh, probably through... I'm sure it is through medical school, I'm sure they taught us this at medical schools, you're aware of it, but have no idea of how it works, or what it entails.

The BNF was also cited as the place where interviewees first became aware of the Yellow Card scheme – especially by foreign-trained GPs, some of who were regular reporters to the scheme. For some, the BNF was their first awareness of Yellow Card scheme, if they had not been made aware of the scheme at undergraduate level or during postgraduate training. Non-UK interviewees cited the BNF as the place they first came across Yellow Card reports. Others were aware of the MHRA reporting guidance in the front part of the BNF. Interest in the scheme was triggered at varying times, but generally at times when formal training processes were being experienced.

Experience of reporters varied with regard to undergraduate training. All groups of reporters included individuals who had been aware of ADR reporting in their undergraduate training, although interviewees were often unable to remember details of what they had been taught at undergraduate level.

I Do you remember being specifically taught about the Yellow Card scheme at undergraduate level?

R10 Yea, I think I did, as part of pharmacology we did. I'm not sure it was a long time ago, but I think I remember it being mentioned as one of the ways in terms of how drugs are developed and how trials are done.

Lapsed and regular reporters described such teaching in terms of “upbringing” and mentioned positive role models, sometimes named, linked to clinical pharmacology training. However, the non-reporting interviewees recalled ADR reporting within undergraduate studies.

N5 We used to have pharmacology lectures from XXXXX XXXXX and they were always entertaining sessions. I remember them well. I used to take part in them when I started work as a GP practitioner, I actually used to start some of the teaching, and er, yes being told about the Yellow Card system in those days, as an undergraduate.

I You mention undergraduate days..

N7 *I remember being given a lecture about it. I remember there were also bits of the BNF that fall out and you had to push them back into the BNF, so they have always been quite Yellow and obvious. I have always been aware of them, but just haven't used them, but I remember in the lecture being told that they existed and they were important. That's all that I remember from that lecture which was eight or ten years ago.*

Some reporting GPs were unable to remember any undergraduate training.

L3 *I kinda guess it must have been, but I can't remember. It's a long time ago, since I was an undergraduate. Awfully, long time ago.*

R7 *I can't positively remember anybody particularly teaching me about the Yellow Card Scheme, it was quite a long time ago, but nothing sticks in my mind in that vein.*

Most foreign trained GPs had not been educated about ADR reporting, with the exception of one GP who had attended lectures by a renowned world authority on pharmacovigilance— and who had maintained his interest in ADRs.

Most regular reporters and lapsed reporters noted that they had received postgraduate training on ADRs, usually in discussions or educational meetings concerning prescribing issues. Non-reporters had rarely come across the Yellow Card scheme in postgraduate education, although one interviewee described an occasion when a mentor had suggested the scheme to her during GP training after she had described an incident involving an ADR.

N7 *No, it hasn't actually, it hasn't come up since and yes, I guess, throughout the rest of my training it's never really been thought about. I guess when I was a GP registrar, I asked my trainer about this particular reaction and whether it was worth reporting or not. He encouraged me to report it and that is about all that I can remember really. But I generated that question, I wasn't otherwise told about it.*

Interestingly one non-reporting GP had been previously involved with the original West Midlands ADR study group running in the early 1980s, but was now inactive in relation to the Yellow Card scheme.

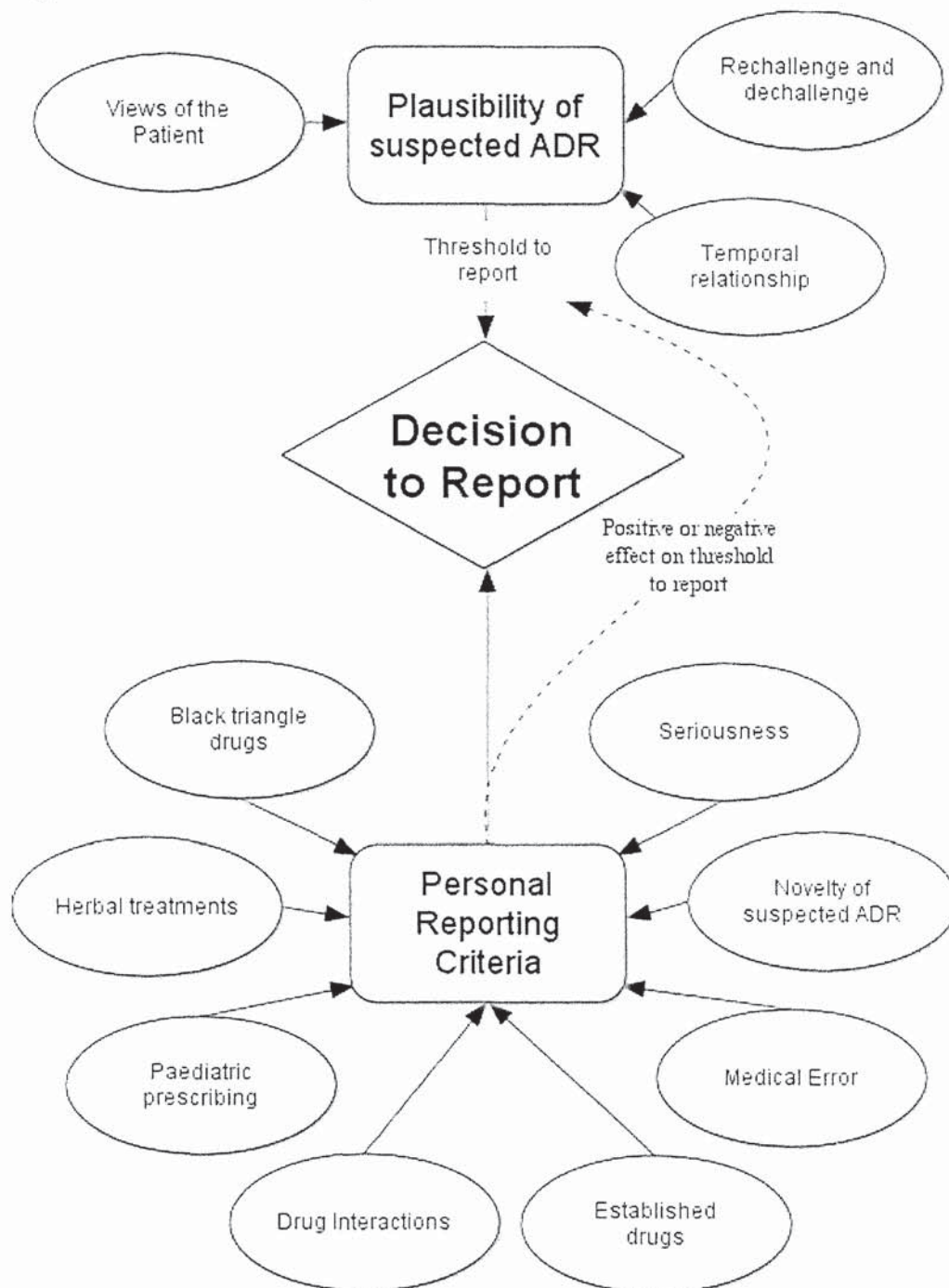
Many reporting GPs had some active involvement in postgraduate or undergraduate training.

6.4. *Making the decision to report*

Once a reporter has an awareness of a suspected ADR, assuming some knowledge of the Yellow Card system, a decision will be made on whether or not the report will be reported to the regulators.

Interviewees had personal reporting criteria, which were based on the factors relating to the drug, the reaction, or the patient. The conceptual categories that contributed to this personal reporting criteria are set out in Figure 6-2. In addition to a suspected ADR meeting the interviewees personal criteria for reporting, the GP would also have to make a decision as to the plausibility of an adverse reaction. Plausibility was affected by the views of the patients, potential rechallenge or dechallenge with the suspected drug, and the temporal relationship between the suspected ADR and the drug concerned. Crucially, interviewees exhibited differing thresholds for plausibility, which could also be affected by the reporting criteria. For example, a reporter could have a lower threshold for reporting a serious reaction to a drug.

Figure 6-2 : The decision to report an ADR



Further elaboration of interviewees reporting criteria and assessment of plausibility are set out overleaf.

6.4.1. Plausibility

Plausibility of a suspected ADR being related to a drug was a key factor in deciding whether to submit a Yellow Card. Not all regular reporters reported suspicions, and there were admissions of filtering reactions sent to the Yellow Card scheme on the basis of judgements about plausibility. The threshold of plausibility before completing a Yellow Card varied.

L9 *I don't think I'd have to be sure at all. I would err on the side of reporting if in doubt. I've heard Dr. Ferner [Director of the Yellow Card Centre WM] say that in a lecture - "If in doubt, report. We'd rather get more and then be able to look over the data we've had up to now." So I tend to report if I think of it at all.*

L7 *I like to feel it's more than just you're waiting for a patient when you start them on the drug to say, "When I started that drug, this started to happen." You're almost wanting that, or when you start a drug, something changes, whatever, so you're wanting a temporal - a clear temporal relationship almost, aren't you? You don't want to just - you don't want to overuse a symptom with just sending off them willy nilly, so you do want to have something that - yeah, you don't want something where you say I believe this is a side effect because of that. There must be some sort of chain I think that you must see, so yes, I suppose plausibility is what you're looking for.*

Some reporters demanded certain reactions, others were more willing to accept less certain suspicions. Interviewees who noted the importance of reporting suspicions for detecting new safety signals, still admitted to filtering reactions that were submitted to the Yellow Card scheme.

L9 *You've got to make a judgment, I suppose - is it truly the drug, or is it something about the person, and the placebo effect of the drug making them feel that they're throat is closing up, their skin feels itchy, or whatever. A lot of the symptoms can be very nebulous. I think if there's not much to see, and they're not unwell, I don't think - I wouldn't report something like that. I think it probably got to be something that I'm convinced is there. So there's a lot of value judgment going on.*

Plausibility was sometimes judged on a potential and theoretical pharmacological basis for a suspected ADR. Some reporters noted that their relative lack of pharmacological knowledge meant that suspicions based on patient views and temporal associations were more important than those suspected ADRs, which had a mechanism. Confounding factors were also used included in assessing the plausibility of a suspected ADR.

R4 *I think it has to be very plausible really. I think that if it is just something that you feel isn't related to the drug, or something co-incidental, I probably wouldn't report that, but I think I report things that are related in time to the use of the drugs really, so you would have to be plausible in sort of the relationship of the timing of the drug and major enough to be worth reporting really. I'm not sure I would know plausible in terms of the way the drugs work,*

As well as characteristics that might be used in ordinary causality assessment interviewees also noted that the plausibility of a reaction could be based on a patient's history and/or patient characteristics. Patients with a history of complaints about drug therapy were noted as being less likely to be experiencing a true ADR. Some regular reporters were aware that their filtering of reactions by plausibility was disadvantageous to the Yellow Card Scheme.

R5 *I'd probably report if I had a suspicion, but it still has to be fairly plausible, in a way that is sort of related to taking the drug. Lots of people who are on drugs just have things happening to them. If they have been on the drug for a while already then it might or might not be related to it. [...] Indeed and not only from a biological point of view, but also from a previous knowledge of the patient, you know that's obviously the beauty of being a GP. There is an a priori likelihood of this being a true problem. We've got whingers and we've got non-whingers. If a non-whingers comes in and has something then it's likely to have some real biological entity. If a whinger comes in, it can have all sorts of stories, and it's very unlikely to present true physical pathology, which is what GPs do.*

When discussing how sure they would have to be to report a suspected ADR, non-reporters exhibited a slight tendency towards looking for higher levels of plausibility or a logical pharmacological basis.

Some awareness of filtering the cases this causes, but this was tempered by a concern about wasting people's time by submitting a report which was un-associated with drug use.

N2 *Yeah, Oh right, OK, I think in my opinion I'd have to be pretty sure that it was a reaction due to the drug as opposed to the illness otherwise I'd be wasting people's time.*

6.4.1.1. Temporal relationship

The timing of a suspected ADR in relationship to the use of a drug was important to all interviewees. This temporal relationship was used both as confirmation of a suspected ADR and refutation of a suspected ADR. Obtaining a good history from the patient was deemed

important by many interviewees. The temporal relationship was sometimes deemed more important than any plausible pharmacological basis for the reaction. Interviewees noted that temporal relationships were the most likely reason for a patient suggesting a drug might be the causal agent for a particular adverse event. Strong patient beliefs about a temporal relationship between the drug and suspected ADR could influence the decision of interviewees to report.

L8 I don't have to have a certainty in my mind that there is a reaction or a connection. If it is a significant symptom and there is a possibility of it being a side effect particularly with a novel drug I will report it.

I As long as you have a suspicion?

L8 Suspicion, yes, that's adequate. Or even a temporal connection between the two, even if you don't necessarily think they are linked I would still report it.

Although many reporters were happy with a temporal relationship acting as the main suspicion for an event, other interviewees were looking for other corroborating data to find a suspicion of a reaction, such as pharmacological plausibility to link the drug with the event. A temporal relationship was rarely the sole arbiter of whether a suspected reaction would be reported, however a lack of a temporal association was universally acknowledged to make a suspected reaction unlikely.

N6 Often it is just something co-incidental, but they can be right as well.

N5 All you can do is look at it, and if somebody has started something new, if there is a temporal association, when they started it and they developed some new symptom or sign, then it just raises your index of suspicion, doesn't it.

6.4.1.2. Rechallenge and dechallenge

Re-challenge, the practice of re-administering a drug to a patient to see if a suspected ADR re-occurs, was rarely mentioned by interviewees. Regular reporters mentioned re-challenge as an ideal, but accepted it was not normally practical. Interestingly, re-challenge was mentioned as important by two non-reporting GPs, one of whom would use re-challenge regularly when patients had (relatively trivial) reactions she felt were not biologically

plausible – perhaps indicating higher standards of evidence before accepting the validity of a patient concern.

R10 The name of the drug, what the reported effect was, and whether there was a clear cut association between the timing of the events and whether the patient got better when they stopped it. But ideally you'd like a re-challenge, but it's usually not practical.

N7 Or with a very strong link in time. If it was out of the blue and they had never had this problem before. And it was linked with a drug. If it sounds biologically implausible, and say it is unlikely, give a week to go back to normal and we'll restart it and if you get the same problem again, then we will stop it for good. And I often say things like that I suppose. If I think it is unlikely to be linked.

The resolution of an ADR following the discontinuation of a drug (dechallenge) was also viewed as raising the plausibility of a reaction.

L3 So the last one I sent the guy was very clear that his symptoms were related to this medication and he'd experimented a bit by stopping and starting and was absolutely clear in his mind that it was a problem and it certainly wasn't listed on anything I got, so I sent that one in.

However, ADRs that had resolved before the GP had time to assess the nature of the reaction themselves, were on occasions discounted. Although interviewees found patient views useful in assessing a suspected ADR, there was evidence that GPs applied a filter to reactions – both in terms of what they considered plausible, and what they felt should be reported to the Yellow Card scheme. Patients were viewed as unrealistic in attributing causation to a drug, and vague nebulous symptoms were likely to be attributed by GP to the placebo effect. Some reporting doctors preferred to see physical manifestations of suspected ADRs themselves, and could be sceptical of resolved ADRs reported by patients. Professional opinions were thought necessary to validate the patient's opinion. Interviewees would generally only report reactions that met their criteria for reporting, rather than trusting the initial view of the patient on causation.

L9 When patients just report in, "I stopped the drug two months ago because I had a funny round lesion on my leg, and when I stopped the drug, it went away." I think if I haven't seen it, and it's been a long time, I might not be convinced. So if it was something unusual that made my ears perk up - but I think if the timing is wrong, I

don't think I would, no. I think it would have to be enough that they came to see me, and I kind of directly related to it. I know I've said things have happened on the phone, but I think mostly those sorts of things are side effects. I think probably what helps you report is if they're sitting in front of you, and you think that's odd and report it.

6.4.1.3. Views of the patient

Interviewees considered the views of patients to be important. Patients were often the communicator of initial concern about a suspected ADR, although the GP may have to make the connection between the drug and event.

L5 Erm, yes, they do come. They come in two ways. [...] either the patient's acknowledging the reaction and stopping the tablets even before they come, or turning up with the actual problem when you diagnose it yourself.

GPs noted that patient reports of suspected ADRs could be provoked by media reporting of drug safety issues or lists of ADRs supplied to patient in Patient Information Leaflets (PILs).

R4 It depends on the patient. I saw someone today who wasn't someone I initiated, but came in with the piece of paper with everything underlined. You know, the patient information leaflet with all the symptoms underlined that she had sort of had. And that happens not frequently, but not infrequently either. Patients do come...

Some reporting GPs gave “permission” to patients to report ADRs, by asking the patient to be wary of the risk of ADRs or warning that a drug was new (sometimes explaining the black triangle). They would specifically ask them to report back on their experiences.

R3 Yeah, I've always said to patients if I am giving them a medication, with every medication I give you there could be a reaction. Now I could give you a long list, and you can read the paperwork in here, but I think this is the safest medication to help you with your condition, but if you have a problem with it you must report that back to us.

R1 Yes. Whether patients report or not depends in part on the permission you give to report a problem. [...] So people do report spontaneously but far more, but you'll get far more in the way of reports if you ask people directly about what has been happening to them since you last saw them, about problems etc.

This practice was considered important by those GPs that did it, because patients may not feel comfortable about raising a failure of treatment or non-compliance with them otherwise.

These reporting GPs argued that without actively eliciting patient opinions, suspected ADRs would not come to light.

No interviewee noted an example of a patient asking them to complete a Yellow Card, although some reporting GPs did raise the issue of making a Yellow Card report with a patient. In those cases, no examples were given of patients objecting. Indeed, some patients were pleased to know their experiences were being reported. This tactic may also have re-enforced the commitment to ensure the card was completed.

As well as judgements about the pharmacological likelihood or importance of a suspected ADR, interviewees also assessed the nature of the reporting patient. Some patients were viewed as “*whingers*” who commonly complained about treatments. Reports from “*whingers*” reports were taken less seriously than reports from “*non-whinger*” patients.

I Do you always accept patient reports as reportable?

R6 I think I wouldn't report every time they report an adverse drug reaction, but yeah, I try to kind of work out if there is a time and causal relationship between when they started the drug and when they got the symptoms, because I think sometimes patients, you know there is a placebo effect, isn't there? When you have got a patient who thinks that there is a side effect, they'll get side effects, or if they have read the datasheet they might come up with side effects.

Concern was expressed that only those loud enough to complain were likely to come forward, or patients with higher educational status might come forward, with quieter patients suffering in silence. The strength of a patient's views on the association between a drug and a suspected ADR was a factor that was taken in consideration by some reporting GPs.

L? I think if it's, you know, way down in the list of possible side effects, and this person had it obviously, I mean enough to come in and report, "I feel like this on it." then I would report that in.

Some non-reporting GPs also reported patients putting forward suspected ADRs. A Non-reporting GP also reported that he has had patients complaining about drug side effects, when

he felt they were due to disease symptoms. So, both reporting and non-reporting GPs act as gatekeepers to the Yellow Card scheme.

6.4.2. Reporting criteria

No one set of interviewees consistently described the MHRA's criteria for reporting ADRs to the Yellow Card scheme and GPs held differing views on what should be reported or what they would report to regulatory authorities.

R6 Life threatening things, definitely. What else? And I suppose unusual things really, but I certainly wouldn't report every dyspepsia with a non-steroidal or every ache and pain that people get with a statin. You know.

Regular reporters described criteria similar to that of the MHRA criteria for reporting, but usually not in detail.

R2 I suppose if I saw it in a case where I was surprised I would report it. So if it's an existing drug with well known side effects, I wouldn't bombard you with reports of something I think is widely known, so I think that would be my criteria. So if a thing I think is not known or if it's with a new drug were obviously all reports are useful I think that's my criteria.

R3 On one occasion, I had a patient who died quite suddenly, and there was no obvious cause, but this patient had had Diflucan on several occasions prior to death and I think had had some sort of liver problem, and it was never put down to the Diflucan, and I just wondered how those sort of issues were dealt with in such a way and I reported this to the CSM at the time because I just felt it was significant. We just recently have had a patient who had, a young woman of 28, who had a heart attack, who was on depo-provera, and that was the only medication she was on. So I've reported it, we've reported that, clearly reported that as an incident like that to the CSM system.

Reporters tended to have their own criteria developed from their perception of what is important to the Yellow Card scheme. Even with these self-defined criteria, reporters noted that there was a difference between theory and practice, with reporters failing to report suspected ADRs even according to their own criteria.

R1 There's going to be a difference here between theory and practice. I hope I would definitely report any thing that had resulted in a death or anything that has resulted in a hospital admission, but I'm conscious already that there's one I've had and I haven't done it.

Filtering of reactions was apparent, with GPs making value judgements about what is important – either in terms of effects on the patient, or what they think may be of interest to the MHRA. Even with regular reporters to the scheme, this could mean serious reactions, leading to admission to hospital and/or death, were not being reported.

Regular reporters demonstrated understanding that all suspected ADRs of new drugs should be reported. Lapsed reporters maintained similar criteria to that of regular reporters, with awareness that if there was any doubt about what to report a report should be made. A bias against reported common known ADRs was apparent, with a concentration on what the reporter considered unusual.

L9 So I would not report something that I felt was within my understanding of the common known side effects of that drug.

The unusualness of a reaction could be based on the knowledge or experience of the reporter, rather than the current level of knowledge in the literature. An example being angioedema associated with ACE inhibitors in comparison to haemorrhage associated with warfarin; although both are known and well documented ADRs angioedema was deemed more reportable than haemorrhage – perhaps indicating more personal experience of warfarin's ability to cause haemorrhage.

L6 Angioedema I would still send in, I wouldn't send well know reactions like haemorrhage with warfarin.

In addition, reference sources such as the BNF were used as a method of examining what is a more unusual reaction, with things that are "way down the list" being more likely to be reported.

L9 But if it's more unusual and low down in the list, I think that I should report this because they may not be aware that it's happening as much as it is.

Some reporters expressed a fear of reporting reactions, which might be seen as trivial to the regulator. One reporter noting that a tick box existed on the current Yellow Card which asked

if the suspected ADR was life threatening or serious; this led to them questioning the importance of reports they were submitting.

A lower threshold for reporting of newer medicines was apparent. Some reporters report any reaction to black triangle drugs, but most did discriminate again on grounds of unusualness of reactions. The appearance of confounding factors associated with a reaction was also given as a reason, which might prevent a report. For example, a patient with risk factors for heart disease suffering a myocardial infarction following the commencement of a COX-II inhibitor.

A bias towards serious events was apparent, but several interviewees expressed an opinion that serious predictable ADRs to established drugs were of less importance to regulators since they were already well documented. Established drugs are seen as less of a priority - with any interest focused on serious ADRs. However, serious suspected ADRs which were common or predictable events associated with the drug were viewed of less likely to be reported. An ADR caused by failure to monitor treatment was also frequently discounted as a reportable reaction – which was on occasion linked to the issue of the definition of an ADR.

Non reporters demonstrated a relative lack of knowledge of MHRA reporting criteria. Some attempted to guess what the criteria – suggesting a focus on new drugs for which it was assumed that less information was available.

6.4.2.1. Novelty of the suspected ADR

The unusualness or novelty of a suspected ADR increased the interest in reporting to the Yellow Card scheme amongst reporting GPs. The BNF was often used as measure of what is unusual. ADRs not listed within a drug monograph were considered more unusual, although as already noted the novelty of a reaction could be based on the GPs own experience.

L9 Yes, I think - because I think my way of viewing adverse effects - if it's something that I know frequently happens and is described in the BNF, then I would not necessarily report that as an adverse reaction. But if it was something new that I didn't know about that I had never used before - and I might look it up in the BNF - say they'd come up with something odd, you know, a strange looking rash, incontinence, or something odd, I'd look it up in the BNF. Yes, I would report it if I'd never come across it before.

Previously unlisted ADRs or unusual reactions were listed as another reason for reporting, whereas well-known or common reactions were less of interest. For example, myalgias associated with statins were not reported by one regular reporters as they were considered known effects. Well-recognised reactions were not perceived as adding new knowledge to drug safety.

R2 So if it's an existing drug with well known side effects, I wouldn't bombard you with reports of something I think is widely known, so I think that would be my criteria.

Well-established drugs were suggested to be less likely to cause new reactions, but some regular reporters were aware of the potential for novel reactions with more well-established drugs.

R8 Of course it depends on the type of drug, obviously black triangle drugs are more important, but again you might find something that's different, that hasn't been found before, in something else.

A counter argument put forward by one interviewer, suggested that that GPs would be unwilling to report an event not seen before in the literature, because they would be concerned about their suspicions being wrong.

R1 My experience is that the things that happen for the first time, some doctors are very reluctant to report, because they say this hasn't been reported. They say this isn't a reported side effect, but it's not a reported side effect, even with established drugs, because no-one has reported it because it's not a side effect. Report it, and in my view it should be reported, and let people at the other end sort it out. Whether it's relevant or not.

6.4.2.2. Error

Non-reporter interviewees did not see error as part of the reporting scheme. Examples of ADRs occurring as a result of, or partly involving, error included failing to monitor the

effects of drug therapy, thereby putting the patient at risk (e.g. failure to control INR and a resultant haemorrhage), the use of a drug outside of its licence or in contravention of labelled contra-indications.

I If there is an element of mistake, like a badly managed INR then you don't think it is reportable?

N3 No, no, it is not reportable, but I would go nuts and ring the consultant, hey are you trying to kill my patients.

Non-reporters, and some reporters, viewed these types of action in terms of operator failure, rather than a failure of the drug itself.

I Say for example, there was an element of error, just thinking of one off the wall, someone is prescribed daily methotrexate and the patient has died. Would you feel willing to report things with that element of error?

R9 Well, I would sort of feel that was my fault really, I mean it wasn't really the drugs fault.

I What about something more subtle, something with a contra-indication or a warning perhaps?

R9 Yes, well I probably would, if I felt it was important then I would. If it was a well known contraindication and the patient was unlucky, then I'm not sure if you are interested in knowing that.

The additional element of error also increased concern about sharing data with third parties— with concern expressed about relationships with other professional staff and examples of NHS staff involved in medication errors being subject to disciplinary procedures.

N4 I would think it unlikely that people would be honest enough to report everything, because we have got bad enough when we try to do within the PCT with significant events. The ones we analyse, non of them are that significant really, because unfortunately there is still a blame culture here, and I know working in a PCT, they are looking at it, and in fact it happened to a couple of nurses who reported very honestly, after giving the wrong vaccine to a patient and it has blown up quite disproportionately, saying about well, we need to investigate in order... but then people get picked on.

So I still find unfortunately, the NHS has still got this blame culture. So within practice, when I do appraisal visits a lot of things happening, they don't mind telling me, but they don't want to tell the PCT. So people always report it, in my appraisal, everybody's appraisal has some significant event, some complaint, but really I don't think people will be that honest, because the blame culture will still be there.

There was also concern that drawing attention to fatal ADRs by reporting warfarin deaths may be preventing reports because a fear of invoking the coroner.

R9 I suppose one of the particular worries I have is warfarin being used more and more, in quite elderly people and I think adverse reactions to warfarin are very under-reported for a variety of reasons, probably because they don't want to excite the interest of the coroner.

Regular reporters would still report even if an element of error was included and some particularly targeted serious preventable ADRs, such as haemorrhage to warfarin as being particularly important to report.

R7 No I don't think so. I can think of the odd dispensing errors, two incidences of dispensing error in the last few years, neither of which were the cause of any harm or side effects, but you know, a patient occasionally comes in with his tablets and its not what's been prescribed. But in one of those cases, someone will have a reaction, the error wouldn't have stopped me reporting.

These cases were seen as important for the purposes of clinical governance, although there was some concern that the MHRA might not be interested in the case of well-known contra-indications.

6.4.2.3. Paediatrics

Many interviewees showed a lack of awareness of the MHRA criteria for reporting reactions in paediatrics, drawing no distinction between paediatric and adults. There was awareness that children are at risk of ADRs and of the high use of unlicensed medicines – and therefore gave the view that reporting was of importance.

6.4.2.4. Drug interactions

Drug interactions were spontaneously mentioned by a number of reporters as a reportable event to the Yellow Card scheme.

L3 or maybe if there's drug interactions that crop up. Then you want to know about those potentially.

Some reporters argued that they would not report drug interactions listed in the BNF.

6.4.2.5. Herbals

Even regular reporters to the Yellow Card scheme were unaware of the MHRA's interest in reports of suspected adverse events associated with herbal products. Some guessed that such reports would be welcome when asked and expressed the view that the Yellow Card scheme was a sensible place to make such reports.

I Would you report and adverse reaction to a herb to the Yellow Card scheme?

L5 I wouldn't have with St John's Wort or anything, I wouldn't have know about reporting that actually. If you are telling me I should be reporting them, I will, So you can do it?

Some GPs felt no organisation was interested in such reports and it was difficult to know where to report herbal reactions.

R4 Interesting. Reactions to herbal products have been seen by both myself, and my partners here, we have had problems reporting. No one seems to want to know about problems with herbal drugs. I can't remember, Xxxxxxx had problems reporting herbal drugs, no one was really interested, no one wanted to know.

Some only thought about reporting after prompting, and did not view herbs as a similar risk to medicinal drugs.

N3 No, I wouldn't. I wouldn't give it that much gravity really. I always thought herbs were herbs.

Some interviewees noted that they had seen an increase in the use of herbal treatments, although there was concern that patients do not always tell them about non-prescribed therapies. There was some evidence of ADRs to herbal preparations being reported by patients to GPs. Interviewees did not always ask patients about their use of herbal treatments, and were concerned about their lack of knowledge in this area.

R6 I think that is a really tricky area, because we haven't got any training in herbal medicine and alternative medicines and it's not going to come in the formulary on our computers as an interactions. I worry about that, that somebody is taking ginkgo biloba or ginseng or something. We are going to get an interaction and I won't know about it, and patients don't always volunteer about something they are taking and we haven't got time in ten minutes to ask them what other things they are taking, and even things like Cod Liver Oil capsules, and all these things that people take and

multivitamins, we re not really sure that that might have an impact on the treatments we are giving them.

Concern was expressed that some patients may have been incorrectly diagnosed due to lack of knowledge about herbal treatments the patients were taking. Some GPs showed awareness of past herbal safety issues, and awareness of the risk of contamination of herbal products.

L2 But we don't get a very great many, but occasionally, but yes antennae are alert when people say they have been taking health remedies of one sort or another, I think mainly because in Guy's, some years ago, in dermatology, some child was taking a herbal remedy and got hugely deranged liver function. I say to the patients, you know the stuff in the BNF ain't all that wonderful, you can get side effects from it, but at least it has been monitored and assessed and given a licence, whereas the herbal remedies from the Chinese herbalist may be quite toxic without being aware.

6.4.2.6. Awareness of the black triangle

Lapsed reporter and regular reporters reported awareness of the meaning of the black triangle symbol – used to indicate a drug under intensive surveillance. Of the reporting GPs, only one lapsed reporter was unaware of the black triangle symbol. There was widespread understanding of the reporting criteria applied to black triangle drugs, including the reporting of relatively trivial ADRs.

R1 I try to report those that are triangled, you know new drugs, anything that happens on a new drug in fact I would on a good day report. And anything I regard as serious, anything the patient volunteers you know and is unusual and not something that's commonly,

However some interviewees had their own interpretation of the meaning of the black triangle, such as “high alert status” or an “extra caution medication”. Some interviewees suggested the black triangle status of a drug was an indication that the drug may have increased potential to cause ADRs.

It was noted that GP prescribing systems do not all flag the black triangle status of medicines, and interviewees noted they would check in the BNF for the status, or make a guess on how new the drug was.

Knowledge in the non-reporting group of GPs about the meaning of the black triangle symbol was lower. Even those with some awareness of the symbol had difficulty explaining its meaning with regard to the Yellow Card scheme.

N7 Black triangle drug I've heard of it, but I guess I don't know much about it. Is that the one where you want to know more about it? I suppose you can't give me the answers now... I imagine that is a new drug that you particularly want to get new information on, I guess it was.

One non-reporting GP noted that the symbol was used to indicate dangerous drugs.

N3 Yes, these are the drugs that have the dangerous reactions isn't it?

It is important to note that non-reporters would cite the fact that a new drug might be a reason to report a suspected reaction, even when they were not aware of the black triangle itself.

L5 I would temper things by the newness of the drug. Just say it was one of the COX drugs, I don't use them any longer, but just say it was or say maybe a hospital had put someone onto one of the COX inhibitors there and they had a haemorrhage, I would report that because there's a slight question mark hanging over them at the present time so I feel it would be an important piece of information to go to somebody, to go to an organisation like yours.

The practical application of the GPs own views of the black triangle scheme were mostly in line with that of the MHRA, with the symbol being used as an indication that there was a lower threshold for reporting suspected ADRs to black triangle drugs than more established drugs. Some interviewees noted that they were mainly focused on the reporting of suspected ADRs black triangle drugs to exclusion of other drugs - unless seriousness or usualness was also apparent.

R7 I find that reporting as I do not terribly often, but I do use the scheme is tend to concentrate on black triangle ones when people are telling you something fairly sort of trivial or un-exciting, so that you're not going to actually change the drug so I report those,

6.4.2.7. Well-established drugs

Both lapsed and regular reporters held similar views about well established drugs. Some felt that reporting well-documented ADRs to established drugs was of little use to regulatory

authorities since they were "standard" reactions within the understanding of the current knowledge of the drug. Reporters expressed concern about "bombarding" the regulator with well-known reactions. One example given was the example of gastrointestinal bleeds associated with NSAID not being reportable as so well known, although other reporters felt that such reports were very important.

I Would you report a serious well-known reaction? For example haemorrhage with warfarin?

L5 I wouldn't bother reporting that and indeed with a NSAID I wouldn't report that either just because it's old hat now, we've known about that for 30 years. You know, so that is just par for the course almost.

Sometimes awareness was demonstrated that the reaction to an established drug was significant, but there was a failure to connect with the Yellow Card scheme.

L7 I think that is partly it. People on warfarin do bleed, and I suspect that they bleed a lot more than is recognized, and so yeah, I think it's fine because sometimes there's a confusion about - do you think that well, you sent them into hospital, they die in hospital, and the hospital should have reported it, which I think is - that's an excuse, sometimes because it's a well recognized complication. I suppose we just didn't quite think of it at the time. It doesn't - the yellow card doesn't come into it particularly in your train of thought.

For some reporters the seriousness of a reaction could trigger a Yellow Card report, even if it was a predictable and known ADR of a well-established drug.

I What if it was quite a well-documented reaction to a well established drug?

L8 I probably wouldn't report it, but if it was serious I would. Let's say if I had a patient on amiodarone who went into liver failure I would report that, even though it is well-established reaction, if it was a minor event then I wouldn't.

For others the labelled and predictable reactions (such as bradycardia associated with a beta-adrenoreceptor blocking agent) were not reportable even if serious in nature. Serious known reactions that were less predictable (such as liver disease associated with a drug) were considered more reportable.

6.4.2.8. Seriousness of report

Both regular and lapsed reporters viewed the seriousness of a suspected ADR as important when deciding whether or not to report.

R1 I wouldn't report something that's commonly reported as being a common problem to a well established drug, so somebody comes in with indigestion on an NSAID I wouldn't write a report, but someone who is admitted to hospital with a gastrointestinal bleed, needing 4 units of blood, I should report.

As well as the value placed on more serious reactions by reporters, it was also noted that more serious reactions were more likely to be brought to the attention of a GP by patients, and more easily diagnosed by the doctor.

Seriousness was mainly defined as hospitalisation, life threatening reactions and death. Other forms of serious reactions included those that were serious from the patient point of view – such as extended periods of time taken off work or significant patient distress. Reporters made their own judgements about what was serious.

L10 If it were a mild bleed like a nose bleed, or a minor bleed then I wouldn't make a fuss about that. If someone was hospitalised with a bleed, then I think I would report that.

R2 What's serious? Well, it's on the yellow card system, a question that do you regard it as serious. You know, is it life-threatening, did it result in them being hospitalised, etc I suppose rather than serious in most cases is if it is a significant thing, most of the side effects are transient. And recover when the person stops taking it. So one wouldn't necessarily say they're serious. Seriousness for me would still be as the Yellow Card says, somebody going in hospital, somebody having a life-threatening event. So I think I would say it is more significant side effects from the patient's point of view, even though I know they're reported them or even stopped the medication, are better or made a full recovery.

Seriousness was cited as a factor in deciding when to report, when other factors affecting the ability to report existed. For example, an interviewee noted that he would make the effort to report a serious reaction when busy, when a trivial reaction in similar circumstances might be left un-reported.

As previously noted, there was awareness that suspected ADRs reported to black triangle drugs, or new drugs, do not need to be serious in nature.

Seriousness may lower the threshold of plausibility for reporting. The more serious a reaction, the more risk the GP will take in submitting an ADR that does not seem plausible. There was an increased willingness to report serious well-known reactions, in comparison to trivial well-known ADRs.

There was variation on the necessity of reporting serious well-known ADRs to established drugs – some interviewees noting that they would not report. The effect of seriousness as a motivator for reporting was attenuated if the reaction was well known or predictable. ADRs that were viewed as a failure of routine monitoring, dosing, or predictable drug interactions were judged non-reportable or even failed to be classified as ADRs.

The Yellow Card currently has tick boxes in which the reporter can indicate if they think a reaction is a serious or life-threatening event. One interviewee noted that these boxes made her question her own views on the seriousness of the reactions she was reporting – leading to doubt about whether or not to report when having to decide to tick the box about seriousness.

L9 And you've got the choice of saying yes or no, and then if it is yes - but I always read this, and I think mine isn't anything near any of that really - because you know, "died" or "prolonged inpatient." So they're rather dramatic, aren't they?

[...]

Sometimes when I look at it, I think that perhaps I'm referring or reporting something rather trivial because of all these questions - "Was it life threatening?" and "Did they have to go into the hospital for a long time?" significant disability - medically significant." And very often the stuff we see is not that critical.

Non-reporters consistently raised seriousness as a criterion for reporting when asked to describe what should be reported to the Yellow Card scheme.

Reporting GPs considered that serious reactions were relatively rare within general practice, and their initial discovery would usually be by secondary care upon admission of the patient. Alternatively serious reactions would be referred to secondary care for management. There was a view that the hospital staff were likely to have submitted the ADR via the Yellow Card

scheme. Fear of submitting a duplicate report was cited as a reason for not reporting such reactions.

L7 If I sent somebody with a cerebral bleed who I thought was on warfarin, I probably should report that. When you think about it, the hospital at the time should already be reporting, and I probably should, shouldn't I, according to their staff, but you don't want to double report something, so it multiplies the ill effect on it necessarily. I presume you've got to organize ways of sorting that out.

Other interviewees expressed concern that some serious reactions were not being reported.

There was also a concern that delay in finding out about the occurrence of serious reactions may occur due to communication difficulties with between primary and secondary care.

I What about well recognised serious reactions? Haemorrhage with warfarin?

L3 Yes, well you are supposed to do those, in real life if they are doing that then they have landed up in hospital and I suppose when I realise it's happened, when I see them 4 weeks later I don't think to fill the card in then.

6.5. The act of reporting

6.5.1. Reporting habits

Interviewees described habits in relation to the completion of Yellow Cards. Frequently regular reporters would talk about the importance of completing cards within a short time after discovery of the ADR. Some explained that if the Yellow Card was not completed immediately then the moment would be lost and the ADR would be forgotten. Completion of the Yellow Card would be undertaken in the consultation, or the surgery session. The temporal relationship between the finding of the ADR and the action of filling in the card was cited as crucial in determining if a card was completed.

R9 I try to do everything when it happens, because it is very difficult to go back to do anything really, whether it is discharge letters, yellow cards or any sort of referral form.

R6 I do it at the end of a surgery or you know, I'm called out to see somebody and I think that's an adverse reaction and I do it there and then, but then I am a bit like that, I clear my desk every day kind of person, I can see that a lot of my colleagues might think about reporting, but not get round to doing it.

Interviewees cited examples of how this had led to failure to report. Regular reporters also used reminders if the report could not be completed at the time of the ADR discovery, either on notepaper, post-it notes, or on a Yellow Card upon which brief details (such as the patient identifier) would be written.

R2 A Yellow Card reminds me, I suppose, I might get a card out and put the patient's number on it, and it's there sitting there saying "You haven't done it yet"

One reporter kept a log book in which he would detail ADRs, which would later be sent in a single batch when time was available. There were some personal anecdotes that these habits were changing due to other pressures with the surgery, with one reporter noting that he was now filling in Yellow Cards 2-3 days after ADR discovery, rather than the same session. There were examples of reporting habits being broken by changes in personal circumstances or changes in the working environment.

R2 I don't think they do because, because I think its important that I make the effort to do it say at the end of the session, or come in earlier to do it, like today, when I come in to do paperwork before the surgery opens. I'll do it then. That sometimes delays it, whereas a few years ago I would have filled a card out in the same surgery session. Now, it might be a couple of days later, I'll make either an electronic or a paper note to myself to do it, and even put the patients ID number on the card, but leave the rest for later. So sometimes, I fill the card in two or three days later whereas initially I would have always been doing it on the same day. So it does make a slight difference,

Some of those completing Yellow Cards did so in consultation with the patient. This informal contract to do something about the ADR experienced by the patient may act as a mechanism of ensuring a card is completed.

Lapsed reporters also exhibited similar habits with regard to Yellow Card reporting. Some interviewees saw completing a Yellow Card as an automatic process, in that discovering a ADR would trigger a search for a Yellow Card.

L9 I don't think so. I think you either - it's part of your everyday practice. I don't think anything would push it down the list for me. But if it's one of the things you've never done or very rarely think of, then I think other things would get in the way. I think if it's part of what you do, like signing a script, you know, or printing it out, then you just think about something that has gone wrong with the drug and report it.

L10 No I don't think so, it is mainly a bit of duty and something I have always done, so it is automatic really, so I don't think there are any factors that would influence me

Again the temporal relationship between discovery of an ADR and the reporting of an ADR was cited as important. Completion of a Yellow Card at, or around, the time the ADR was found was seen as crucial. It was noted that sometimes the insight an event may have been drug-related can arise later, sometimes after the GP noticed a series of cases leading to multiple reports.

L7 Sometimes - I think with the Norplant, I think I just end up - I'd seen three or four, and then I thought, "This is just ridiculous," and then I think I reported all four. I got the details and stuff, so again, that's a credibility thing, isn't it?

Some lapsed reporters did view Yellow Card completion as an administrative task, rather than an immediate clinical issue, placing reports in their in-tray for completion with other administrative tasks.

L7 Certainly you wouldn't do it in surgery. If a patient had a side effect from this drug, I think I wouldn't be doing it then. I'd see it as an admin task to do with other admin tasks, so it fights its way through the pile.

Regular reporters and lapsed reporters were unconcerned if they had incomplete information on dosing of drugs, drug history, or the past medical history, with the suggestion that the noticing of the suspected ADR was important to the MHRA even if some details were missing. They were confident that the MHRA would get back to them if necessary.

L1 I usually fill it in one go and I send it off, even if I think I should have done a bit more work on the doses, but I just make a guess, not a guess, but I say, OK sign. But I think it is better to have some information and you can always come back with your queries.

This was in contrast to non-reporting GPs who were concerned about submitting reports with missing or incomplete information, which might lead to requests for further information.

6.5.2. Role of the BNF in relation to the Yellow Card scheme

The British National Formulary often arose spontaneously in discussion with interviewees.

The BNF was viewed as a trusted and unbiased resource by interviewees.

R6 Vitally important for every doctor to get unbiased information. Like the BNF, if they stopped giving us the BNF I'd be horrified.

L4 I mean I think the - I think the difficult - one of the difficulties of sort of a clinical practice and staying up to date is adding that to one's sort of practice formulary or the mental steps that you take before prescribing a medicine. And I think the BNF is very good because it tends to incorporate that into it so it's up-to-date

The BNF played a number of roles in the management of suspected ADRs and their reporting to the Yellow Card scheme.

Firstly the BNF played an educational role, as noted in section 6.3.4.

The BNF was used as confirmation of a potential ADR and a reliable source of knowledge about ADRs and drug interactions. GPs also used the BNF side effects contained within drug monographs as a ranking system of importance of ADRs, with those further down the list considered the more unusual.

The BNF was always used as an aid in deciding whether or not to report. GPs would check to see if a reaction had occurred in other patients, by consulting the BNF. Some noted that if a reaction or interaction was in the BNF they would be less likely to report the reaction since it was known. One regular reporter suggested that the MHRA reporting criteria could be changed to ADRs not listed in the BNF, Others used the fact the reaction was in the BNF, to give them the confidence to report a reaction. For some it is the only source of knowledge about what are new drugs since GP computer systems do not indicate black triangle status.

Lastly, the BNF was commonly cited as a source of Yellow Cards. The BNF was frequently described, as the first place Yellow Cards could be located. Even those reporters who held a supply of individual Yellow Cards to hand used the BNF as a place of last resort to find Yellow Cards. Even non-reporters showed awareness of the Yellow Cards in the rear of the publication.

R6 Because I always have the BNF on my desk. So it's there, but I used to keep a sheet in my filing cabinet, but with the Adverse Drug reaction Bulletin which I used to get free

and then you had to pay for it, didn't you, you used to send Yellow cards through with that as well. I used to keep Yellow Cards in my filing cabinet, but I expect you can get them off the internet nowadays but the BNF is the simplest way.

L1 I still like this very much [opens BNF at Yellow Cards] if you do out-of-hours service you just rip it out. Don't give that up.

L2 I can't remember when the Yellow Cards went in the back of the BNF, but before they were sort of knocking about, they came in a loose stack in an envelope and you had to sort of find one to fill it in, but since they were introduced into the back of the BNF, and you can just, it's to hand, you can tear it out and just do it, that is the biggest improvement, easy availability.

6.5.3. Online reporting

There was very low awareness of electronic reporting amongst all groups of GPs. There was still considerable preference for paper-based reporting.

L10 I don't know, often filling out forms, computers are not easy to do and I mean we are doing them all the time. It seems slower than doing it on paper form. Which seems ridiculous but maybe it is partly because we don't do it very often and the other thing is that what we tend to do is have the patient screen up there and we write off the patient screen, which of course you can't do if you have to keep flicking backwards and forwards to the patient record which is, you know....

The physical process of getting card had become a reminder/habit. In addition, cards were filled out while looking at patient details on screen. Even those expressing some interest in the online form noted how the online form might be off-putting.

R2 Whereas, online I'd be more likely to do it, immediately after the consultation, when the information is fresh which is better, but its actually the time to switch into another aspect of the computer, and go on line and log it, its going to take a little bit more time in the middle of a busy day, and so that's probably why I haven't done it, because I'd have to remember to do it at the end. And without either an electronic task, or paper sticking up there saying remember. You know?

Use of an online form required switching between tasks on computer, which was seen as harder and more time-consuming than writing details directly onto a card. Some GPs saw their typing skills as limited, and writing was perceived as easier.

R7 It's more time consuming, typing in something by hand. I suspect of course that once you have got that up on screen, that some of the other details on screen you have to then switch the details back to look at the patient and put the thing back in. Whereas when you have got the patient notes up on screen you can just put the details straight down on the Yellow Card.

There was some negative experience of the early MHRA electronic reporting system. One GP had lost heart with Yellow Card reporting, after sending in several reports that were not acknowledged by the MHRA.

R8 And then it became kind of an automated system on my programme EMIS, and when I initially tried to do it, it didn't work. And I think because it wasn't linked up correctly electronically. I think I kind of lost heart with doing it at that point to be honest.

Several GPs raised the idea of a semi-automatic reporting system, which would merge data from the consultation and patient data into a form that they could review and send off. Forms with unpopulated fields into which data had to be entered manually were unpopular and viewed as carrying few benefits over a paper-based form. Some expressed concerns about data confidentiality if data was automatically gathered from the surgery's computer and expressed concerns about the secure transmission of data. Resistance to computers was apparent in some regular reporters.

6.5.4. Views on the Yellow Card

Regular reporters generally considered the Yellow Card to easy to fill in, taking little time to complete.

R6 I think it's very clear and simple to fill in. I tend to use the ones that are at the back of the BNF.

Some found the additional information and drug history sections “fiddly” and laborious to fill in, although the reasoning behind the request for such information was understood. Some found the card did not provide enough space to pass information on.

L8 Not a lot of space on a Yellow Form, the actual logistics of it. It's a bit cramped to be writing down a little bit of history. But otherwise it is fairly user friendly.

R10 Well, it doesn't ask for a lot of information, but it is a bit fiddly filling in all the dates, the doses and the this and that, but that's the minimum information you need isn't it, if it didn't have that.

Lapsed reporters appeared to have a more critical view of the card and the information it asked for. Some found the card easy to fill in general, and not intimidating, with talk of a few

minutes being needed for completion. However one interviewee noted it took him 40 minutes to complete a Yellow Card. Another noted it was quite a “a job to fill in” and pointed to fields such as weight, patients taking large amounts of concurrent drugs, and cramped space for writing in large amounts of information. Writing long lists of drugs, or long medical histories, was seen as a chore.

L5 You must bear in mind that people who have got multiple problems could be on 12 different drugs. And I mean really to put that down longhand - you don't feel inspired to do it.

L10 I think they are OK. It's often a bit of chore to fill in, the difficult bit is filling in the drug history because you know it asks when the drug was started and all of that which can be ... A patient has been on a drug for many years, can be quite difficult to trace back the initial... I mean it is much easier now, all current prescriptions are on the computer system and we can look back about 8 or 10 years. If the patients been on drugs prior to that, I have to say I don't usually get the paper notes out and try and trawl back through those to see if somebody has been on hypertensive for 15 years.

The paper Yellow Card also allowed partial completion of reports, which then acted as reminders and could be completed later. Sometimes this occurred because of a desire to wait for a final patient outcome or sometimes due to lack of time within the consultation.

Non-reporters had less practical experience of the Yellow Card. On asking their views of the Yellow Card views were mixed with some describing them as clear and simple and others finding them too detailed or time-consuming. The number of fields was also seen as onerous. There appeared to be some concern that reporting without completing all fields was off-putting; in contrast to reporting GPs who felt comfortable sending in Yellow Cards with missing information.

N1 If you are a thorough type of person like me you want to fill in all the available information, I know it says you don't have to but if you are going to do then do it properly.

N2 The additional information, you'd have to go through all of this and look it up and maybe ask one of the partners and someone else who's seen the patient, because I don't like sending things off unless it's complete.

Some expressed fears of using the form incorrectly and therefore incurring further obligations as noted previously.

6.5.4.1. The Green Card as a comparator

Interviewees regularly, and spontaneously, brought up the Green Card scheme, run by the DSRU, as a comparator to the Yellow Card scheme.

Regular reporters saw Green Cards as more onerous and annoying, and expressed reduced motivation to complete them. Interviewees described having less ownership of the scheme, due to the decision to report on a card being taken by another party. Green Cards were seen as an invasion into their time.

R4 I find them more onerous and more annoying. I tend not to do those really. I tend to be better motivated with the Yellow Cards because I'm the one doing the reporting and also I don't know what sort of role that has, as a sort of private thing really.

Green Cards were not seen as difficult forms, but retrieving the information was seen as more time-consuming and difficult, interviewees noting the retrospective nature of the events being recorded.

I You mentioned green cards and yellow cards. How do you rate the green cards?

R7 Much more of a pain. Yeah, it is. Partly because it is after the event, with a Yellow Card something has caught my attention while I'm doing it and you know I'll usually do it immediately after that consultation so patient records are there, everything is on the computer, you know, the cards in the BNF, and with a Green Card it happens sort of retrospectively, there may or may not be anything to report so you get the notes crawl back through a period of time through the screen, see if anybody else has seen the patient get more complicated and more of a burden.

There was some evidence that interviewees were making value judgements about which events to pass on to the Green Card scheme, even though the Green Card scheme operates on the basis of all adverse events occurring being assessed. Even some of those making these comments felt strongly enough about the importance of the scheme to complete Green Cards.

Lapsed reporters also saw Green Cards as tedious and requiring more effort to complete. The Green Card was seen as too big, with longer periods of time being suggested for completion than a Yellow Card.

L8 Green Cards are a bit of a headache. They are time consuming. I've got four on my desk now, that I have got to get round to doing, but they are very time consuming because you have to look at previous drugs, over the past twelve months. To do the job properly with a Green Card is quite time consuming and as a busy GP I've got four sitting there and that is the best part of an hour's work if you do them properly and I just haven't got time to do them at the moment.

There was evidence of less enthusiasm for the Green Card, with examples of non-completion of cards. Even after expressing concerns about the Green Card, some lapsed reporters still completed the forms.

L7 I suppose they're more intrusive in that they come whether you want them or not, and often you've got nothing to report - most of the time I've got nothing to report other than maybe people have stopped the drug because they didn't like it for no particular reason. I don't - I would not like it to expand dramatically. It'd end up in the desk and that's it.

Non-reporters were aware of the Green Card scheme, and considered them too large and too consuming to complete. Difficulties were mentioned in completing them, since the move to electronic records meant they had to be completed at work. One interviewee noted that the Green Card scheme had led to him avoiding the prescribing of newly marketed drugs.

N4 Probably, that also put me off, I seldom prescribe brand new drugs. Because all these forms keep coming in from some professor somewhere, it's a nuisance. And it doesn't fit in the normal Lloyd George record as well, so if I don't get rid of it, it causes great hassle for the staff.

6.5.5. Other reporting schemes

A few reporters noted that local critical incident reporting schemes or significant event reporting might be useful to promote the scheme to peers, with examples of case studies involving adverse events and mention of the Yellow Card scheme.

R6 I think if we had a critical incident report related to an adverse drug reaction in the practice we would discuss it our, we do four meetings a year for critical incidents,

somebody would say have you Yellow Carded it, so it might actually enhance the reporting of Yellow Cards.

6.6. Personal motivations for reporting

6.6.1. Personal ownership and responsibility

Lapsed and regular reporters considered the personal ownership they had of a suspected ADR important if they were to report. Calls for information about adverse events they did not generate themselves were viewed as invasion. The personal ownership allowed reporters to make the sacrifice of reporting, which they were less likely to do if they felt they were being told to submit a report. This was articulated by an interviewee describing his relative lack of interest in completing Green Cards.

L2 I suppose it is because I haven't generated it, it's somebody telling me it is something to do. But I do fill them in, but God they are a pain.

Reporters also felt a responsibility to report ADRs. In some cases the involvement of other doctors or specialists changed the perception of whose responsibility it was to report.

R6 I suppose I as a GP you do tend to use your limited range of things that you use for paediatric patients and I had one young girl who was six year old who was on a permanent ventilator and had lots of problems. The paediatrician was prescribing lots of things that that I felt "Oh, I don't know about this" but then he was taking responsibility for the prescribing. She had developed adverse reactions, would I have reported it? No, I would have expected him to fill it in. But it is just as important with kids to record adverse reactions.

The use of complementary therapies chosen by patients also led to a view that responsibility to report was not in the GPs hands.

L6 I don't feel responsible for herbs, if not listed or very severe then might report.

One GP who was a regular reporter suggested that his experience of shared patient lists was that responsibility to report an ADR to regulatory authorities might be diluted. This view was not found in other reporters.

R9 I think part of it is the move from individual lists to combined lists, there's hardly any individual lists left, and small practices left, so when you get a patient seeing 3 or 4 different doctors, no one takes any responsibility to do anything,

because it is somebody else's responsibility. [...]Because they all share the responsibility so the patient becomes anonymous, the responsibility is diluted.

One GP explained that the use of the Yellow Card scheme was part of a process of moving responsibility to a third party.

R10 A moral duty? I don't think I'd say moral duty, I think responsibility I'd put it as and it's also a sort of way of way delegating responsibility. There you are, I've done my bit. Somebody can, if I report it I don't have to be responsible for it, it has gone to the authorities. I suppose that's a way of looking at it.

6.6.2. Duty and reporting

Regular and lapsed reporters both expressed opinions that the reporting of suspected ADRs was a professional and moral duty. Doctors were argued to have a duty to protect the wider community and that the duty towards the Yellow Card scheme should be altruistic in nature. Reporting ADRs was seen as an ethical duty. The scheme was described a "politically correct" in a positive manner and also as a charity. The discovery and sharing of important safety data through the collation of reports was seen as a benefit to the medical profession and society in general. These values were in some reporters instilled at undergraduate level, or by mentors during early medical training.

R1 I suppose what I'm saying to you is that I'm philosophically convinced that it's a good scheme, and both in terms of morals and education, I think it is a scheme that should be supported and that I suppose is product of my exposure to post grad medical education in the past isn't it?

The duty to report was also expressed as an obligation based on the role that a doctor played in the prescribing of medicines.

L5 I think we have got a professional duty, the only thing is does your own internal button get pushed. It gets pushed with me if it is a new drug

L2 You feel that the CSM ought to know about it. I think I'll quote the Duke of Wellington really, the price of peace is eternal vigilance.

Some reporting GPs expressed surprise that any prescribing doctor could not see the obligation they were under to report suspected ADRs and viewed Yellow Card reporting as an integral part of the process of prescribing.

L8 *I can't imagine a doctor that prescribes, not being interested in reporting. To me that seems incredible, I can't understand that. You know, we poisoning people, I mean I've poisoned people. It is always done with the best of intentions, but we poison them.*

Duty was directed at the wider community "it matters for more than your patient potentially".

R8 *I think that would be very useful. GPs are obviously different in their motivations, we are all different and some people will be very motivated altruistically, if they understand that the information is being utilised and how it is utilised then that would help them to do it. Other people can do something about it. So no, I think although there are a large number of people who'll be driven by the financial aspects, I think a lot of us, certainly I do feel that its just as important for the benefit it is going to give our patients, and the outcome of better health in the future.*

In the process of reporting GPs expressed satisfaction from reporting ADRs, which can be seen as a non-financial reward for the reporter – based on their own values and beliefs about the importance of the scheme.

R6 *I feel almost smug when I send a report in, that I'm doing my duty, for unbiased recording of information about medications.*

Non-reporters were less likely to spontaneously raise the issue of duty to report, but when prompted could give idealised views on what would be seen as idealised professional behaviour.

N5 *When something has a price tag you are more likely to do it, but I still think that if we are talking about patient safety we should all be concerned enough to do it whether we are paid or not and I still think that if it is a scheme that people, if somebody is saying this is something we are taking much more seriously and we are doing and using it much more, then just improve the functionality of the IT.*

Financial and resource implications for ADR reporting were more likely to be raised in contrast to reporting GPs, with more support for financial incentives being expressed.

6.6.3. Guilt

Both lapsed and regular reporters described feelings of guilt with regard to ADRs. Firstly, as a result of the moral duty they felt towards the Yellow Card scheme, some reporters reporting embarrassment at not reporting as often as they could, expressing annoyance with themselves when they did not report, or their conscience as a reminder of the need to report suspected

ADRs. Even though both lapsed and regular reporters were high performers in terms of Yellow Card reporting, they were often dismissive of their own reporting rate, considering themselves to be under-reporters.

L5 I think the value of the scheme is very very great. Not to put to fine a point on it, but it's very very great and I'm almost embarrassed in having to confess to you not filling in a form more often.

While this guilt may have been elicited because the interviewees were being interviewed by a representative of the scheme, there were comments that showed that failing to report led to guilt.

L3 The Yellow Cards take a couple of minutes either with the patient or at the end of surgery or when my conscience pricks me and I think I should have reported that.

The second form of guilt was one felt towards the adverse consequences that patients had suffered as a result of treatment they had prescribed or less specific concern about the large amounts of drugs being prescribed in their practice. Interviewees described poisoning their patients, even though prescribing was performed with the best of intentions, and seeing adverse effects in a patient was described as soul-destroying.

R3 So to see a patient have a massive haematemesis who's got an arthritic condition in one joint that's you know, could perhaps have been managed a different way, is pretty soul destroying to see them in hospital and what they have to go through.

This guilt was manifested also as a strong responsibility to report the reaction the patients had suffered. Reporting was seen as part of a causal chain of events starting with a prescription.

L9 And it's important that the information - all this data is looked at because without that - and that all seems absolutely right, and I feel very convinced that we have a responsibility as prescribers to monitor that. I suppose I'm a bit of a nihilist when it comes to prescribing. So I think, you know, the harm that is done needs to be known about, so it's just part of my philosophy that if you are gonna prescribe, and things go wrong, it's important to monitor.

Some reported that they felt there was a tendency to over prescribe medication and that a balance should therefore exist between the prescribing of drugs and the reporting of ADRs.

R1 I think we over prescribe drugs and I think that we need in order to have a balance approach to drugs I do believe that we should be documenting the adverse reactions and the adverse effects of what they do.

6.6.4. Interest in ADRs.

Reporting GPs tended to have an interest in ADRs. One GP noted his own experience within a clinical trial, in which he experienced an ADR, as an event that had led to his interest and awareness of the possibility of harm from prescribed medicines.

R3 I think part of it actually happened for me when I was a medical student, I was taking part in a clinical trial. I had a reaction to one of the medications I was given as part of a trial and hadn't really asked any questions or really found out about what I was being given at the time. I thought it was just great fun that we were involved in something like this and then I began to realise that it wasn't such a good idea to be assuming that anything you took would be safe.

In some, interest appeared sustained due to early exposure to the drug safety issues, developing interest at undergraduate level in clinical pharmacology and drug safety. Interest in ADRs appeared to be tied to a more general interest in prescribing issues.

Not all had a background interest in clinical pharmacology. Others noted a broader interest in sharing information with others, and shared practice. One interviewee mentioned that her interest might be due to family's involvement in pharmacy.

6.7. Barriers to reporting ADRs

6.7.1. Concerns about ADR reporting

There were few concerns about medico-legal issues. Trust in the Yellow Card scheme was apparent, as well as knowledge about the confidential nature of the scheme.

R2 The information is analysed so that centrally nobody can identify that patient. The identification numbers we use are our own computer number within the practice which isn't known outside of the practice. So, we don't use the NHS number, or anything else that would give that information to a third party. It's anonymized and I can't think of any other concerns that would be a danger or harmful, as it were, to the patient.

Patient consent was also not a concern to reporters. Some concern was raised by a non-reporter, who professed ignorance about who got hold of the data and what it might be used for.

6.7.2. Time pressures

The effect of time pressures was apparent on GPs. Many reporting GPs spoke of pressure of work, and a lack of "slack" within the working day.

R8 *That, also the time it takes, quite often we are totally and utterly, I mean today's a good day, we haven't got a clinic this afternoon. I don't need to rush anywhere now for my children, etc. I'm not going for any therapy this afternoon, I've lost of health problems myself, I've got a slot were I can speak to you. But I've got sitting on here. I've got all these notes to summarise, I've got all these various things to do, and this is a quiet time of year. I mean I am not totally full at the moment, and sometimes we just, you know, you get home, and most paperwork has to be done here because it is on the computer.*

Even those GPs who felt they were doing less work, due to reduced commitments to an on-call service for example, noted that time pressures continued in the working day. Many regular reporters noted that time was not an issue preventing them reporting.

R5 *Oh yes, always time pressure. It's twelve o'clock and I've already finished my work for today, apart from the baby clinic. OK, if I am alone my partner is on holiday and I see forty patients in a morning, there probably wouldn't be a Yellow Card, but even then I'd put it by for later if it is really interesting. Really, it doesn't take long reporting.*

There were examples of regular reporters changing their reporting habits due to time pressures.

R2 *I think yeah, I think the, I think the pressure of work is... anything extra that has to be done, has to be justified, you know, have I got the time to do it. I think the amount of slack in the system, is far less than it was 20 years ago or even 10 years ago, so we have a more restricted working day, once we get into the day.*

R8 *But you will get quite often, you will sort of be in here on a Saturday or Sunday trying to catch up on paperwork, working until midnight at home, doing stuff like that it is extra stuff like working until midnight at home, doing stuff like that, so extra stuff is just for me, kind of if it can be avoided, just avoid it.*

L3 *I think we are busier, I don't think it has effected my reporting, but I can see a really hectic surgery perhaps the person with a potential side effect being seen in surgery*

with a whole load of other people to see, particularly at the end when you are seeing people quickly, that might be the thing that stops you, stops me reporting.

Lapsed reporters also viewed time as important. There was also a view that the working day was becoming more pressurised and intense – with fewer breaks when opportunities to complete odd tasks could be taken.

L5 The 10 minute appointment system which means we are often seeing patients for three hours a day, the fact that I have got my repeat prescribing which takes me an hour and half a day, and my paper which takes me an hour a day, if not 2 hours a day. So you know, you can see very quick that there just isn't any time, just the sheer volume of the work. It might also be tied up with the fact that also as I've become an older practitioner, my patient group has got older as well, and therefore I am not dealing with coughs and colds anymore, everybody who comes in to see me has got multiple pathology, rheumatoid arthritis, plus ischaemic heart disease, plus the diabetes, and really to shoe-horn anything into 10 minutes is really very very hard indeed.

Some lapsed reporters noted this was impairing their ability to complete Yellow Cards. Others noted that the relative rareness of Yellow Card reports and the simplicity of the card meant that time was not the factor preventing reporting in their cases.

Non-reporters noted that time pressures and workload had increased and that there was pressure on GPs both in and out of the consultation period. Time pressures were seen as a factor that would reduce the chance of a suspected ADR being reported, although ADR reporting was considered a more time consuming activity by non-reporter.

N2 you know running around like a lunatic at the best of times, you haven't got time to fill in extra forms, and it's just another form to fill in isn't it?

6.7.3. Administrative pressures

Regular reporters noted that pressures have changed in general practice - with a greater emphasis on administrative work.

R4 The pressures in general practice have changed. I think it's harder to remember to do everything, there's a lot more you are doing for the patients and a lot more sort of paperwork and administrative work that you are doing, so it does get harder to remember.

Some reported additional administration being completed at home; coming in to work at the weekend or working until midnight at home. However, many interviewees noted that the ability to shift work to home had also decreased with increased computerisation – leading to increased pressure on the working day. Paradoxically, improved communications were suggested to be adding to time pressures and administrative tasks, as the GP would perform a task, rather than support staff.

R2 So we are already beginning to integrate with the hospital. Those sort of things are also a time pressure perhaps. That, whereas, if something was missing from a patients records, meaning there wasn't a letter or they haven't sent us a report, instead of picking up the phone now I do it electronically. And that's both a blessing and sometimes gets the information faster, but always means you are doing it yourself, whereas two or three years ago I would have asked a member of staff to pick up the phone. And then when the information was through, the patient would either speak to me on the phone or come, but now I tend to do some of that myself in the consultation. Again, it's a another pressure.

Limited administrative sessions meant that Yellow Cards can be left in preference to a referral letter or completion of another task.

Lapsed reporters also reported an increase in administrative aspect of general practice.

L5 Yes, a huge amount of administration. Yes, that's gone up really since the new contract came into being a year or two ago, that has gone up hugely really.

But also noted the increased levels of administrative staff employee within surgeries. There were suggestions that the job of a GP had become easier in some respects by the loss of an on-call service, but this was balanced by the increase in administration due to the new contract. Increasing computerisation of the general practice environment was also seen as some thing preventing administrative tasks being complete at home.

L10 Yes definitely, I think the daytime is more intense, but then you finish at whatever time. We are now hoping to have a home link to our computer system, so that you can do some of our work at home in the evenings, because there isn't enough time in the day to see the patients and get all the clinical work done.

Non-reporters similarly felt administrative tasks were increasing within surgery time, with not enough time to deal with written work and computer-prompted material. Although many

noted this was linked to the new contract, one GP noted this was a trend started in 1990 with the introduction of the internal market, and GP workload had not recovered since.

N5 It started in 1990 with the introduction of the internal market into the NHS because hospitals suddenly dumped a load of stuff that they weren't going to get paid for back out into primary care and our workload doubled if not tripled overnight with the contract which was imposed on us then. And it's not really recovered much since I would say.

It was felt that financial aspects of general practice had become more prominent and there was an increase in competing pressures with general practice.

6.7.4. Priorities

Regular reporters were finding it harder to remember to complete all tasks in their work.

There was a sense that they were performing a lot more individual tasks for each patient, in terms of paperwork and administrative tasks.

R9 Yeah, well I mean, in the old days, you just saw the patient, dealt with what was wrong with them, gave them a prescription or not, told them what to do and that was great. But now there are so many other things, these little boxes that come up and tell us what to do and a lot of my patients seem to be on the chronic disease register so you have got to try and sort out various things when they come in with their sore throat or chest infection, whatever it is they have come in with. So, there's a lot of other things going on really, not to mention the pestering we get from the PCT, the DSS, and the NICE guidelines.

Regular reporters did prioritise the filling in of Yellow Card reports. Interviewees described a tightening of the working day, with little time in the working day for optional additional tasks. There were examples of regular reporters failing to submit a Yellow Card due to a busy surgery.

R6 I think it is time. We have a limited amount of admin time and if you are very very busy it kinda gets left and its not seen as important as writing a referral letter or completing other information.

Lapsed reporters also reported similar concerns about pressures within the surgery, with concern about extra administrative work pressures mitigating against completion of Yellow Cards.

L3 Well, there's always something important to do. So, it's in the list of priorities, so unless you have decided that you are going to do it, setting it as a priority, before dashing off and doing a visit or to go for a meeting. So it is something that could get forgotten, unless you have torn it out and put it on your must do pile.

Interviewees felt that such pressures would reduce the priority given to the Yellow Cards by GPs, as the Yellow Card may not be viewed as essential and therefore could be forgotten. At a personal level, some argued that completing a card wasn't something that would be pushed down their list of priorities, but even then mentioned that "various things that were there in the old days can often slip by" and that Yellow Cards can fall by the wayside "on days like these". There was some evidence that Yellow Cards may be falling as a priority in the minds of GPs.

L7 I feel like work mitigates against it in the volume, the rates, and all the rest of it and just seeing you is great, because I've got three appointments crossed off, so I'm not seeing patients. It's quite relaxing, but I haven't got many telephone calls to do, and I don't think I've got many messages, so today's quite a good day, but sometimes you're just whizzing through to try and keep up, and another bit of paper, it is extra.

Non-reporters also reported increased pressures in the practice environment and they were already doing too much work, before thinking about adding in Yellow Card completion.

6.7.5. Quality of Service Framework pressures

Reporters to the Yellow Card scheme had differing views on QOF targets. Some argued that targets were leading to more work. Others felt the majority of QOF work was already being undertaken, but that they were now recording more. Data entry on computer systems and validating QOF targets was seen as more "paperwork".

Some found the new contract demoralising and suggested it may be crowding out voluntary activities of an educational or altruistic nature, skewing practice priorities. There was concern that voluntary activities might be forgotten or "slip below the horizon".

R2 We're under so much pressure with the new contract, data entry and so on, our computer systems, and validating the QOF targets are so important that there's an amount of, we still call it paperwork, paperwork, and it makes our days very tight and there's little time to do extra things. So things that are voluntary, I think, get

forgotten. They're on the "I'll do it when I have time" stuff, rather than on the "I'll do that today".

- L10 The increased administrative workload, it's something that doesn't have to be done and just not bother. And because of you know, in a lot of practices the workload has gone up, and with the introducing QOF and so on, it has put pressures on people to do other things that have incentives attached to them. Maybe they don't see it as particularly a high priority in their workload.*

There were differing views on the validity of differing aspects of QOF, some were thought to satisfy administrators and others were deemed clinically important.

- L8 Some of it is a complete waste of time of course, some of it is just target hitting that satisfies administrators and have nothing to do with clinical, what we perceive as clinical benefit, it is more to do with management and politics, but the other kind is clinical and has obvious clinical benefits. That's the more important one.*

Pressure to comply with the contract was seen as pressuring the working day, although those who viewed ADR reporting as part of their daily practice rather than an administrative task felt it was not reduced in priority. Others felt that while QOF was not affecting their ability to report, it was affecting other GPs, and noted the influence QOF targets had on their surgery.

Here a non-reporting single-handed GP describes the pressure of QOF.

- N3 Administration, like for example I have to print out some paper, how many QOF points have I got. Oh, I'm running short of 25% and I have three months to catch up, so I say how am I going to catch up and how am I going to get those patients back in?*

Some viewed QOF as a political tool to, which reduced quality of care by decreasing time for patient interaction.

- N2 QOF takes along time, with all the templates and you are constantly reminded of it by your managers, which is good because we are not aware of it, certainly myself I'm not aware of it. And it has to be drilled into you again and again: we're not filling this in, we're not filling this in. Some of it is very very time consuming, but you know there is a bonus at the end of it. We, are, we are driven.*

Non-reporters had concern about pressures within the consultation caused by the new contract. such as attempting to remember the targets and dealing with computer prompts when talking to patients. There was a consciousness of concentrating on the computer more than the patient.

- N1 *I haven't reported on a Yellow Card in 10 years. The consultation is being squeezed by other considerations. I know people say it only takes a bit of time, but there is hardly any time in a consultation to spare. QOF fields on the computer take time to work through.*
- N7 *I guess I'm conscious about not just looking at the computer really, rather than at the patient. So, sometimes a patient will have gone out the room, and I'll look back and there will be loads of alerts on the screen. I'll have to shout them back in to do their blood pressure or something, so I guess there are lots of things to think about when they are in the room.*

6.8. Strategies for increasing reporting

There was awareness amongst all groups of interviewees that there was under-reporting to the Yellow Card scheme, and individually some non-reporters noted they were aware of not reporting for an extended period of time.

I *Can you remember the last time you filled in a Yellow Card?*

N3 *Oh, good lord. Six years ago.*

Throughout the interviews views on mechanisms to increase Yellow Card reporting by GPs were explored.

6.8.1. Fee for reporting

Interviewees' views on the use of financial incentives to increase Yellow Card reporting were divided into the effect such an incentive would have on their own reporting, and the effect it might have on ADR reporting by professional colleagues.

L9 *It wouldn't increase mine, but it probably would increase other people's, so I'm sure the answer is yes. Of course, it would depend on the fee.*

R2 *I don't think it would increase mine because of my particular interest, but I think it might be something that might get other GPs interested, more interested.*

None of the regular reporters showed any personal interest in a fee for Yellow Card reporting. Some were suspicious of the introduction of a fee, wondering what the motivation would be for its introduction.

L4 *The pros and cons are that you might get over reporting and I think that I'm always wary if people throw money at people because it's normally, it's, you know, sort of an*

obverse incentive, and in many ways and let me think for a moment as to why that might be the case. I think you may sort of - why, you know, I think question is to try to think of it objectively is sort of why are they trying to bribe me because we get an awful lot of bribes to follow priorities that are not particularly our priorities by politicians.

For some, the introduction of a fee degraded the ethical reason for reporting to the Yellow Card scheme; with some examples of reporters suggesting their interest would fall in the scheme upon introduction of a fee.

I Do you think a fee would increase your participation?

R6 No, it might put me off, but I think it would increase other people's participation.

I In what way would it put you off?

R6 Erm, I don't believe that we should be being paid to do that part of our job, I think it is part of our job as a doctor, to be participating in this scheme, the Yellow Card scheme.

Some expressed shock that other GPs would expect payment for what they see is a professional obligation.

L8 You are kidding, that is no good. It's part of your job, you are prescribing these drugs, you need to report them.

The fact that reporting was seen as an intermittent and relatively rare event, made some feel a fee was unlikely to motivate them. Some were happy without payment, unless they were asked to report outside of their own criteria.

L6 Serious reactions rare - reporting is not effected by workload, since only do one or two a year. If you want all my cases of hyponatraemia to be reported, you'd have to pay me"

Others noticed a change in the professionalism of medicine.

L1 Any many GPs, not so much me, they think I am not going to do anything without getting paid, the whole attitude is changing, from a more, what do you call it, professional attitude to, yes, we bill whoever we can bill as long as it lasts, until we get privatised.

Some reporters mentioned infectious disease notification, which does attract a fee, and noted that the fee was not a motivating factor since it was too small.

R5 *No. Not really terribly. I think there would be better methods than a fee. When you report the notifiable diseases, that's gets a little fee for that. It would be very difficult to make the fee high enough to really interest GPs. You know that's, I'm sorry to be blasé about this but that's not the problem.*

However, even interviewees who felt that their ADR reporting was not financially driven felt that fees for Yellow Card reporting might drive up interest in the Yellow Card scheme. Although the ethical and professional duty was felt to be enough in their own practice, their personal experience of general practice, and historical understanding, suggested that GPs minds would be focused on a financial aspect to the scheme.

R8 *GPs are obviously different in their motivations, we are all different and some people will be very motivated altruistically, if they understand that the information is being utilised and how it is utilised then that would help them to do it. Other people can do something about it. So no, I think although there are a large number of people who'll be driven by the financial aspects, I think a lot of us, certainly I do feel that its just as important for the benefit it is going to give our patients, and the outcome of better health in the future.*

Despite this, concerns were also expressed about the introduction of financial incentives. Concern was also expressed about over-reporting. It was suggested that fraud might be a problem after introduction of a financial incentive and also "loose reporting".

R8 *You are more likely to get a lot more dross reported from some people. If you aren't using that initial filter, you may need to make the criteria more up front, we just want you to report, things that are not written down in the BNF as side effects, or whatever. Or however you would do it. Or we want to know about drugs that are black triangle.*

Concern was also expressed about the possibly increased bureaucracy required to administer a fee, both at the MHRA's level and, also at the GP surgery level, where other financial incentives had led to the requirement to employ additional administrative staff. Cynicism was also expressed about where any money to fund such a scheme would come from.

R3 *I'd like to know where the money was going to come from. I can't make the excuse that all GPs have had a big pay rise and nurses jobs are under pressure. Obviously, where are you going to get the money from?*

Setting of the level of any financial incentive was also seen as problematic by interviewees. Interviewees, both non-reporting and reporting, gave examples of activities that attracted substantial payments (such as insurance reports at £100 apiece) being put to one side due to lack of time available to complete them.

R1 Well, I hope it wouldn't influence me. And the DSRU pays a fee for long reports, and insurance companies pay fees for reports, but they still get put to one side because of the volume of work; I'm not sure it would work. I'm not sure it would make a difference. The only reason I'm hesitating is that the history of general practice is that if you pay them to do things, they tend to do them rather than the things they do for free. The things that tend to get done, sadly, are things that are either statutory demands of doctors like sickness reports or things that are paid for.

For some non-reporters a fee for reporting was seen as a mechanism to provoke their interest in reporting suspicions of ADRs and payments were described as a driver for GP interest. Some non-reporters still considered that reporting was a duty, rather than a fee-earning activity.

N5 When something has a price tag you are more likely to do it., but I still think that if we are talking about patient safety we should all be concerned enough to do it whether we are paid or not.

Others were more money orientated spontaneously raising the issue of payments to increase their interest in Yellow Card reporting. A single handed GP noted that financial incentives might increase his fellow GPs interest.

6.8.2. Yellow Card reporting target

Early interviews often brought up QOF targets, not in relation to the Yellow Card scheme, so later interviews included a question about a Yellow Card target. Reporting GPs expressed concern about how any target could be set for ADR reporting – given their unpredictable nature and the lack of a clear definition of what constituted an ADR report.

R4 I think the problem is that it is unpredictable isn't it. I mean, it is a very difficult thing to be judged against really.

Widespread concerns about targets and the effects they had on GPs were also expressed. Targets were seen as a “two-edged sword”, which focused GPs’ attention on specific areas, but which could potentially discredit the Yellow Card scheme by moving it from a charitable clinical activity into a business activity or government agenda.

- L9 *The new world of QOF targets - I don't know - I'd avoid it because it's a two-edged sword really. We've got so much to focus on that it would just be another thing that I think would muddy the water of other things. I think this is separate - that this is about good practice really. I don't know - you can't put everything in targets. I mean targets drive you mad, don't they? [...] There comes a point, I think, when it's counterproductive, when you forget about the patient, and all you're doing is ticking boxes.*
- L1 *I don't know. You may, it's a difficult one, because you always, you can also discredit it a little bit, another target, I mean it is something to ask other GPs. [...] It's dubious, I doubt whether that is the way; you have to be very careful if you put it into a target. [...] it becomes part of a business decisions, oh which target shall we pursue? Because we can meet the thresholds, so that is the risk if you put this one in the targets.*

In addition, there was some concern that use of a target would lead to practice management staff chasing reports of ADRs from GPs, and some concern about the nature of the ADR reports gathered from such a process. What was the incentive to report an important reaction once the target had been achieved? The view was aired that such reports might be artificial in nature and skew the data collected.

- N7 *I don't know how you would really make a QOF target, because I think you would be looking out then for things, that might, you know, picking up things, well I suppose that is what you want us to do, I guess I'm worried that we might pick up things that perhaps aren't an adverse drug reaction just to get a Yellow Card sent off.*
- L8 *Oh please no, No targets. No, targets are the bane of our lives, and target driven anything distorts it. So what's the purpose behind it? It distorts the results.*
- R6 *I think you'd get artificial reporting.*
- L2 *You'd probably hell of a lot more chaff, and not much more wheat, so I would leave it out of the QOF scheme.*

Targets were described as political, or trivialising, even though some existing targets were described as valuable.

However, some interviewees expressed the view that a QOF target for reporting ADRs might work, even when they personally disagreed with the idea of one. Altruism was “described as only going so far”. Interviewee R1 suggested a target of ten Yellow Cards a year, Interviewee L5 thirty cards per year.

R1 It's not so much the reward as the finance, Doctors are competitive, and if you sent them a target they will try to achieve the target. GPs are very competitive, partly because they have been competing all their lives. They've been competing to get into medical school, They've been competing to get the best A-level, they've been competing against their peers, One of the things that happened with the points system is that GPs don't want to be seen as performing less well than their peers, so they are prepared to collate all sorts of data they may think is useless in order to stand out well compared to their peers, when the current system was proposed for rewarding GPs by results.

L5 I hadn't thought of that, gosh that's very innovative, because we are driven by targets and you might well find if set a target at each of the practices and you have to say, send in like 30 or so, or something a year if you did that, you could have some kind of payment, rather than fee per thingamabob, that would be interesting. I'd go for that. I don't think my colleague would appreciate my saying it

Others thought a general target of “showing participation” in the scheme would be adequate.

There was greater interest in any financial reward from a Yellow Card target from non-reporters, compared to reporting GPs.

N3 Well, I think it would be a good idea. That would be a way forward. It is a bright idea. It's a very good idea, I think that way, everybody would be in a winning position, NICE, everybody, yeah, that would automatically tell me to look out of it.

There was a view that GPs can be discriminating in the QOF points they chase, based on the amount of money the points would attract, the work involved in obtaining the points, and their view on the clinical usefulness of the points.

6.8.3. Legal requirement

Regular and lapsed reporters were not impressed with the suggestion of creating a legal requirement to submit suspected ADRs to the Yellow Card scheme. It was considered unenforceable due to confidentiality and a lack of clear definitions. Reference was made to disease notification, which also suffered from under-reporting and examples given that

reports were not made when the diagnosis was unclear. A non-reporter felt it might influence his decision to report, although he was an isolated case.

6.8.4. CPD link

There was little support for linking Yellow Card reporting to continuing professional development (CPD). Some viewed linkage of the Yellow Card scheme to CPD as a form of penalisation for non-compliance. There was also concern that changes in the appraisal methods for GPs meant it was difficult to attach CPD credit to schemes QOF was described as the only way to make linkage to GP performance.

I There have been attempts to try and link Yellow Card reporting to continuing professional development?

R1 That doesn't wash anymore because the way in which we are appraised is much more nebulous than that. We are not just collecting points anymore, thanks goodness, the way it..., I mean the sort of points that you could collect points by going to a very meeting/lecture simply by having your bum on a seat. It's much more focused now depending on the prejudice and interest of the appraiser and the appraisee. I don't, under the current system,

6.8.5. Reminders of the scheme

There was strong support from reporting GPs that they should be reminded about the Yellow Card scheme and some concern that the scheme was not publicised well. Interviewees felt that selling the benefits of the scheme was particularly important, more so than reminding individuals about the reporting criteria.

R2 I suppose, one could send out more information about the benefits of having reporting historically, where certain things were observed by the use of drugs in the NHS and in prescribing, but perhaps weren't understood as side effects, and particularly, serious side effects or interactions.

Periodic reminders in the medical press were suggested. Reporters suggested using existing systems within PCTs to remind GPs, citing the potential use of prescribing advisors.

R2 If our chief pharmaceutical advisor was given that sort of information she'd be quite happy to pull a small amount of it in her regular monthly column in a monthly newsletter.

There was also a suggestion that could be counterproductive if used in excess.

L10 the trouble is you don't want to drum it into people too often or people will switch off I think. It's trying to pitch it at the right level and frequency and telling people that it is a useful thing to do.

Some non-reporters suggested they had not heard of any reminders of the scheme.

6.8.6. Reporting rate feedback

Regular and lapsed reporters were mostly in favour of the supply of reporting rates of Yellow Cards to PCTs. Comparison of PCT performance in comparison to national averages was felt to be useful, with others suggesting feedback at the practice level could be useful.

L7 I think comparative data is always of interest, so in the PCT, you do comparative data about things, and that can be quite interesting to see where you are, and if you're about average, you think, "Well, I must be doing this probably about right." It doesn't always have the effect you expect it to. For instance, we're very high antibiotic prescribers and we're one of the highest in the PCT, and we've not managed to bring it down despite the fact that really, we should up - know what I mean, so it doesn't always work, but I think it's of interest. I always like looking at that.

Other regular reporters noted an interest in knowing how they were performing in comparison to the national average. It was suggested that prescribing advisors could be used to communicate this information. Use of such information had to be in a non-pejorative manner. Non reporters were less convinced by the supply reporting rates, with concern expressed about comparisons of practice performance.

6.8.7. The effect of peer pressure and competition

Peer pressure was cited as a mechanism that could be used to improve Yellow Card reporting participation. Comparison was made with attempts to control and improve prescribing within PCTs.

R3 I think peer pressure works brilliantly, if they see somebody like me, who has a clinical leadership role, does have a fairly high level of reporting, they say, if he's OK about putting himself up front and showing the things that happen to his patients, perhaps I ought to be doing it. I think we've looked at this, we've looked at the way that prescribing alters in the PCT

GPs did not like to appear to be outside of what was generally considered good practice or what might be considered the mainstream of the profession.

L8 *I don't think any practice wants to be viewed as being radically different, unless they can justify that in some way, if there is a skew in the population, But for the most of us, we are fairly similar in our demographics, so if your practice is wildly out, high or low for anything, you have to ask why. It doesn't mean you are necessarily wrong, but you have to look at it again to see why you are different.*

Even without financial incentives it was suggested that some issues could be pushed within GP practice by use of non-financial motivators or competitive instincts between surgeries. Some considered that PCTs, and prescribing advisors, could promote Yellow Card reporting in this manner, especially if there was feedback on reporting rates.

Professional isolation within a single-handed practice was noted in comparison to working within a larger practice and there were examples of suspected ADRs and the Yellow Card scheme being discussed within larger practices.

6.8.8. Suggestions to improve reporting

Improved postgraduate education was a common suggestion to raise interest in the scheme, with focus on integrating the Yellow Card scheme into GP vocational training.

R5 *Ah, yes and GP trainers, of course, if you got it in the VTS, vocational training scheme, they have a half day in Wolverhampton, every Thursday half day, for instance if somebody from the Yellow Card Scheme, turned up on a Thursday afternoon, you'd get all the current GP trainees in Wolverhampton and have a chance to get them early. Do that once a year and you get every future GP in the West Midlands, who you have talked to once. I'm sure you would get an invitation if you tried. If you speak to the course organiser, how can they refuse you? You're a very politically correct thing.*

It was noted that formal meetings were less common now, and that the Yellow Card scheme could be fitted into more general education concerned with good prescribing.

All groups of interviewees noted it was important to ensure reminders about the scheme were given, both to raise awareness of the existence of the scheme and also to underline the benefits of the scheme to doctors and the public. Mailings and information back from the scheme were put forward as good reminders; electronic material was viewed as less likely to be read. It was suggested that *Current Problems in Pharmacovigilance* could be redesigned

in order to make it more in line with the *BMJ*, which used boxed summary information, which a GP could find quickly.

It was also suggested by interviewees that the MHRA should make use of magazines that GPs routinely read, such as *Pulse*, *GP*, or *Prescriber* magazine.

Prescribing advisors were a trusted source of information and could be willing to inform GPs about the Yellow Card scheme in their routine meetings and mailings to GPs. Prescribing advisors already play an important role in disseminating information about drug safety to GPs. Some were used by GPs to answer specific queries about ADRs. Although interviewees noted the current focus was on QOF and controlling prescribing costs, a number of GPs viewed safety issues as important.

L8 Our PCT prescribing advisors, for example we have a meeting next week and that would be an ideal opportunity to raise the issue of ADR reporting and perhaps explain how the system works and how the staff do their job and how they relate to us. Because it is probably something GPs know very little about, apart from sending off the Yellow Card and that's it. We don't know what happens after that really, so I think a bit of gentle education really through prescribing advisors just to remind us of the service would be useful.

Some interviewees were keen to see the involvement of pharmacists within the practice and medicines management, seeing reporting as an administrative task which required clinical knowledge.

It was also suggested that increasing integration of the Yellow Card scheme into GP electronic systems should be undertaken. Automatic prompts for reports to particular drugs was suggested to remind doctors of the necessity of reporting, or provision of a specific list of drugs that the MHRA wished to obtain reports for.

R7 If there was a bigger alert, when you went to prescribe one of the black triangle ones, the whole screen went bang this is a black triangle drug, possibly that would make you think... prescribing methotrexate, it comes on like your making a nuclear attack or something. If you really really want to do this, prescribe this toxic drug and it's this great big one with a tiny yellow button to click, so something like that then that would help.

One interviewee suggested recruiting designated practices with a MHRA contract to provide intensive reporting sites that would run in parallel with opportunistic and spontaneous reporting from other GP practices.

6.9. Views on the MHRA and the pharmaceutical industry

6.9.1. General perception of the MHRA

Those reporting doctors aware of the MHRA and its role in drug safety viewed its activities as crucial to drug safety. However, knowledge of the MHRA was poor even among reporters, with some unaware of their role and function, or even their name.

L9 I think I must do - I mean I'm not really that familiar with the MHRA. I probably just haven't noticed their logo on the top of letters. I think I'm assuming I know who you mean, so I just say that really. I will kind of read things twice if it's come from government really, because I don't think they're particularly interested in the nation's health.

The function of committees and commissions within the MHRA was generally unknown. There was also confusion with other organisations names and roles. In particular The National Institute for Health and Clinical Excellence (NICE) was confused with the MHRA, as were the DRSU who run the Green Card scheme. There was relatively higher awareness of the non-defunct CSM.

Positive views of the MHRA came from personal contact with MHRA staff, which they viewed as the local Yellow Card Centre's staff.

R1 Well I can only talk about the individuals I have had contact with, and I have been impressed with their, I mean if I have had a query about whether something should be reported or not, or if there has been something complicated, more data than I can fit on the form, I mean if I want to put a free text letter in or something, I'd speak to somebody up there, and its been very helpful.

Generally reporters held good or neutral opinions about the MHRA.

R7 I suppose frankly they hardly ever enter, but since you ask me, I probably think they doing a good job, they're not, quite frankly, there are some bits of the NHS where you

feel that services or structures are useless or hopeless, I don't think of the MHRA in that way."

L2 Force for good.

The independence of any agency looking at ADRs from the pharmaceutical industry was important to many reporting GPs.

R6 If they are independent of the pharmaceutical industry, then yes I probably trust them.

The MHRA was seen as a counterbalance to the pharmaceutical industry and an organisation that was expected to act in the face of evidence.

R10 I think they probably attempt to counterbalance the forces from the pharmaceutical industry.

L9 I feel I'm reporting to a medical body who then, on the strength of data that they have, will take things further, I have assumed. Otherwise there is no point in reporting. And I trust that I am reporting for the reason that things will taken further if there's clearly an issue about something.

Some interviewees showed distrust of the government, and yet less distrust, or even trust, was shown towards the MHRA as the operator of the Yellow Card scheme. In some individuals, similar distrust exhibited towards the industry was directed towards government input into drug safety issues, with greater trust being given to sources that are viewed as academic in nature.

R1 There's a part of me that says that the further the heavy hand of government is away from these things the better. Because people don't trust government, there's a long history of government spokesmen getting things wrong and things being misinterpreted. We could go back to the Salmonella business, the BSE business, more recently Foot and Mouth, I'm not sure the government wearing the sort of Ministry of Health, Department of Health hat is necessarily the best organ to put this information across, I think that information that is seen as coming from academic institutions that appear to be independent of government is much more powerful. Now of course the government gets its information from academic institutions you know, but some degree of impartiality, some degree of distance between the ministry and the organ that is putting out information I think is beneficial. I think people are destructive, that's a good Freudian slip, distrusting of stuff that comes out from the government.

Some criticism with regard to conflict of interests were apparent, although confusion existed on this point in relation to other bodies, such as NICE.

There was some evidence that criticism of the MHRA in the medical press and mainstream media could affect GP views.

R2 There's in the lay media, concerns about their ability sometimes to effectively monitor new drugs, but it's a very complex issue and it isn't because I think anything of the organisation that I want to either notify them or not. I haven't got any firm opinions, or particular knowledge of their strengths or weaknesses, but I know it's a very complex thing to do and with new drugs, the amount of exposure to patients in research is relatively limited, and the years of exposure are limited and so on, and therefore it's not possible to pick up on unusual side effects until you've got the wider population being prescribed it.

Another GP noted that listening to a Radio 4 documentary about the TGN1412 trial had raised his awareness of the MHRA. Non-reporters exhibited little knowledge about the MHRA, with some recognition of the CSM.

Most had a neutral opinion of the MHRA, although one interviewee noted that:

N2 They are not doing a good job or we wouldn't be having all these problems.

6.9.2. Views on Safety messages and drug withdrawals

There was a general view amongst interviewees that drug safety issues and drug withdrawals were being communicated in a timely manner via the cascade system.

N1 Things are much better these days, we tend to find out sooner than the newspapers these days.

Interviewees described occasions when the media covered a drug safety before they had briefed themselves about the issues involved as annoying.

R4 I think the only frustrating thing with that is that sometimes, it seems to be in the press before the doctors find out, you know when things come down through the cascade system. When there's problems with drugs. Obviously, it difficult to get them out completely before it starts appearing in the press and patients start coming and asking questions about drugs and problems.

Advice from the MHRA in the form of additional information for the management of patients was valued by GPs, who would sometimes keep the information to hand to answer patient questions. The MHRA's advice on HRT was given as an example of a useful document.

Emails from the MHRA were criticised for being badly formatted, containing extraneous material of little use to GPs. The GP had to take the further step of clicking a link within the email to obtain information. Many of the warnings were viewed as not useful, in particular information on batches of faulty drugs, devices and specialist hospital drugs. It was suggested that the high frequency of messages diluted more serious issues of importance to clinical practice.

L10 Yeah, but you get a lot of rubbish to. You get these cascaded emails now, you know you get a report, about six pages, about some chemotherapy drug that has never been used in primary care and never will be, you know six ampoules have been contaminated or something, and I think that spoils it a bit since it is just sent to everybody in the country, whether they have got any interest or are likely to have. And you just wonder could it not be focused on things that are relevant to primary care or secondary care or whatever. It's a good, rapid system, but I just wonder how many people read them. Most of them are very wordy; all you need are one paragraph about the nuts and bolts of it really.

Several interviewees noted that prescribing advisors provided a filtering role, informing GPs about important drug safety issues and withdrawals, giving localised information about management, such as alternative agents, and specific queries from GPs. This role was valued by GPs.

R5 We have got a really good prescribing lead at our PCT and she has really been our major source of information, plus I have a partner who is particularly interested in therapeutics so she also sends us emails around when there is a particular problem with the drug so, something like the COX II's we got quite a lot of information from both of those sources.

Interviewees generally trusted the MHRA's decisions, although on a number of occasions interviewees questioned the decisions taken. Sometimes withdrawals provoked resentment from GPs. The decision to restrict prescribing of co-proxamol, venlafaxine and thioridazine were some examples. Some questioned the motivations behind withdrawals – some suggesting potential conflicts of interest the MHRA might have. There was no evidence that these disagreements had any detrimental effects on the motivation to report suspected ADRs.

6.9.3. Current Problems in Pharmacovigilance

Reporting doctors were mainly aware of *Current Problems in Pharmacovigilance*, or its branding and design if they could not remember its title. Although not all read it fully, due to lack of time, some noted particular items that they had kept to hand within their surgery.

L2 *Interaction with St John's Wort, that's the sort of thing you just tear out and put into your file.*

Sometimes some of the subject matter was considered too specialised.

L8 *Yes, we do get that bulletin, and it sometimes relates to very specialised drugs doesn't it? Hospital based, very specialised drugs. So I try to scan through it and if there is something that relates to us then drawn attention to it, but often it relates to drugs we would never prescribe, or even see prescribed.*

Aside from the material contained with the publication, its supply was also cited as a reminder of the existence of the Yellow Card scheme and its continued importance.

R7 *I think that Current Problems in Pharmacovigilance is a good publication. I find that interesting. We all get sent that don't we? And I would have thought that was a good thing to remind you of the scheme because it's saying here are specific things that are happening to people from these drugs and here's the list of the black triangle ones.*

There was some confusion between *Current Problems in Pharmacovigilance* and the *Drug and Therapeutic Bulletin*, sometimes interviewees suggested that both titles were published by the same agency. Reporting doctors noted that they get in paper format these days apart from glossy medical magazines full of promotional material.

L8 *But I do look at that bulletin, since the demise of the Drug and Therapeutics Bulletin, it's probably the only thing we have at the moment that comes in paper format, apart from Prescriber Magazine - which is promotional.*

The paper format and being delivered at home were cited as points that made the *Current Problems in Pharmacovigilance* more likely to be read. Awareness was reduced amongst non-reporting GPs.

6.9.4. Yellow Card Centre

Reporters to the scheme were largely aware of the West Midlands YCC and aware of the centre's activities. They exhibited some personal attachment towards the local centre.

R7 I feel that I've got some ownership here and some input into a system to people I know.

R4 In some ways it is nicer to have a regional monitoring centre rather than a national one just because it is just sort of, makes it feel more local and attached, rather than being detached from the practice really.

The centre was viewed as responsive to enquires and reports, with one GP expressing disappointment when acknowledgement letters ceased to arrive after he submitted Yellow Cards via the EMIS system, as noted previously. There was evidence of the value of personal relations and positive feedback about the centre's communication.

L4 Absolutely brilliant. If it was some sort of office centrally in London they would never come out and try and engage with the GPs, you know, it's - you can't do everything by computer. It depersonalizes everything and, you know, and I think it's important that something like drug safety should have a human face and try and get as good a speaker and diplomat as you can get.

R1 I think that they are good. My experience of them has been very positive. Having somewhere regional that you can actually phone up if you are so inclined and speak to somebody who knows you as a person, rather than some place in the middle of Whitehall is to me a great advantage.

Feeding into a system where they knew the people involved was seen as motivating, and gave more personal ownership of the process. The personal touch for knowledge of the local centre may have led to a sense of guilt if no reports sent in, seen as letting the people in the Centre down.

R1 I had a sense that I was letting the people in Birmingham down by not sending the forms in. Do you know what I mean? I know that might sound silly, but having spoke to them on the phone, and found them very helpful, I had a sense I ought to send them a card in. I think I'm less likely to send a form in to an anonymous place in the sky.

The YCC was seen to be providing feedback that re-enforced the value of the reports submitted.

L3 *I can remember getting quite an interesting letter back about once, from Dr Ferner, so something that was quite interesting and something they were just looking at so, I thought, Oh, he's obviously interested. And he's passing kind of useful stuff back then.*

Reporters preferentially sent cards to the local Yellow Card centre over the central MHRA address. It was felt that a local centre would be more aware of regional differences in prescribing.

Non-reporters had little awareness of the regional YCC. There were no spontaneous mentions of the YCC centre or its staff in relation to educational events or publications. One non-reporter had previous experience of working with the regional centre in the early 1980s, and felt a local centre was important, however he had no contact with the YCC centre at present.

The majority were unconcerned with whether the card was sent to Birmingham or a central MHRA address, but still noted that feedback is important. A small minority mentioned it was a pity that the change to the local service was occurring.

6.9.5. Acknowledgement letters and further information

Regular reporters and lapsed reporters valued feedback from the MHRA. Feedback was viewed as confirmation that they had been correct to report the suspect ADR and reassured reporters that their concerns were being taken seriously. As noted previously, one reporter (R8) noted that a lack of feedback from electronically submitted reports, had led to a lack of interest in the scheme.

Views on the nature of information provided back varied with some preferring a brief acknowledgement letter.

L7 *I assume you note them down. I assume they're put in some sort of database, which I think is as much value as I'd expect it to get. I think we usually get a letter back saying, "Thank you for your whatever," which I suppose is quite nice, because then you don't want a long letter or anything. I don't want anything deep and meaningful back, but I do want - a little comment is quite nice, but you don't want one with all the things... Sometimes you end up with letters that are a page and a half long, so a short, sharp one.*

Non-reporters generally had no direct recent experience of feedback from the MHRA, but did suggest it would act as a reminder and a form of encouragement. There was however evidence that lack of feedback after the submission of Yellow Cards could have had negative consequences on some individuals willingness to report. Concern that their time had been wasted in completing a report and that they may have over-reacted by reporting a suspected ADR.

While a small minority found the multi-page DAPs interesting to read and useful, most felt they were of little use for future management of the patient and were not sure how to use them. Here a lapsed reporter is asked if he values the DAPs he is supplied with:

L4 I do. Just pattern recognition really. So that you can spot a trend.

Reporters to the scheme had ticked the box for further information about the suspected ADRs they had reported, though not in every case or every occasion. There was a desire from some reporters for less information, more targeted information related to the report the individual had submitted, or lists of the more commonly reported reactions to the drug. Large amounts of paper were not considered useful. Some regular reporters noted the local YCC had supplied scientific papers related to the reaction they had submitted. The currently provided DAPs of aggregated yellow card data were considered too large, confusing and not user-friendly.

L9 I'd rather receive a sort of summary sheet about the drug, I think, and that's stopped me ticking the box from now on. I don't really want more paper.

R3 It might be easier if I didn't get so many pages. It would be easier if I just had a simple A4, this is bang, the sort of side effects, the quantities, an A4 size is probably my limit of actually being able to take in information when I'm given information that I've requested.

Non-reporters had no experience of further information from the MHRA.

6.9.6. Follow-up

Regular and lapsed reporters had both experienced follow-up requests for further information from the MHRA. Follow-up was not considered an onerous task and only occasionally occurred. There was no evidence that experience of follow-up requests impacted on the willingness to report ADRs to the Yellow Card scheme. In some cases, the follow-up was taken as confirmation that their report had been worthwhile.

6.9.7. Independence of information

There was concern amongst GPs about the amount of independent information about drugs that was available to them. The recent loss of free provision of *The Drug and Therapeutics Bulletin*, which was well regarded and judged to be an unbiased non-promotional, was mentioned frequently by interviewees.

L8 *I thought it [Drug and Therapeutics Bulletin] was brilliant, I read it as often as I could. I thought it was a very good publication, very non-biased. Very cautious. Given any doubt they wouldn't go with the new drugs. Very sort of conservative in that sense, but perhaps one should be that way. I thought it was useful, it was a shame it wasn't subsidised by the government.*

Alternative freely provided glossy medical magazines were seen as promotional in nature. Government sources of information were not judged to independent, which had their own agenda. This included even more local information sources such as PCTs, who were seen as more price sensitive than concerned with safety issues.

There was however a perception that contributing to the Yellow Card scheme was a method of providing non-promotional material.

R6 *I value and want unbiased advice about medication and unless ordinary GPs and doctors like me report, we are not going to be able to have that type of information, so to me it's I suppose down to my belief system that all of us have a responsibility to build up that information. It's a base, it's a non promotional base.*

The MHRA, despite being a branch of government, was trusted to act if evidence arose of safety issues, with even those most distrustful of government expressing trust in the Yellow Card scheme. The scheme was viewed as an interface between the industry and clinicians by

some, or as a scheme standing in opposition to the industry. Independence from the industry was valued as important.

6.9.8. Media and ADRs

There was widespread fatalism about the role of the media in drug safety and it was seen as an inevitable part of modern life, even though, as already noted the cascade system had improved.

L9 Finding out from the radio? I think it's part of life. You know, journalists are gonna get hold of things and make it into a story. So it's newspaper or radio - that's modern life, isn't it?

Many GPs had experienced cases of confused patients as a result of media stories. Concern still existed that the media seem to know about safety issues before healthcare professionals, preferring instead if they were made aware before the public.

L2 when I hear it on the Today Programme, when I'm getting up three days before the cascade hits me. It's infuriating, infuriating. I don't know what happens, it should surely be the other way round, just get it out to the workforce and don't send out a press release to the journos.

I Adverse reactions are in the media, do you find that is a problem in practice?

L2 Yes, it can be, it can be, people aren't really that bad, but you will find people coming in, phone calls galore, people saying "What should I do Doctor?" And I don't actually know and I feel a fool, because I am sitting there with no information – it is very exasperating.

Some interviewees felt that patients were becoming more aware of the potential for harm from prescribed medications, and that a larger minority of patients had to be persuaded to take drugs.

R2 Certainly, there are a sizable minority of patients now, who whenever you talk to them about prescribing, they say they really don't want drugs, and I think that is because there has been so much publicity about side effects, disasters, whatever, that people are now very wary, there are some people who are wary. It is a minority, but it is interesting that there's a larger minority of people that I have to persuade to have a drug, than I would have done in the past.

The biggest issue relating to coverage of health stories concerning drug safety issues was the media's tendency to hype safety concerns, and it was thought unlikely that the government could do little to control the situation.

R5 Well, I'm not really sure it is the government. [...] They haven't really got control of the media, which is a good - I like to live in a free country.

The internet was also cited as problem, with patients presenting material from searches in relation to the drug scares.

6.9.9. Value of own report

Regular and lapsed reporters generally felt their reports had value to the MHRA, allowing the MHRA to make decisions about the safety of licensed medicines.

L8 I think they are crucial, because until the drug is out in public use they are still being monitored, the process of making these drugs safe, So unless we fill in Yellow Cards it is impossible to make a decision. I would have thought they were crucial.

Value was expressed in terms of the report adding to a larger body of evidence.

R4 Yes, I think so. It is difficult to know, but I have sent quite a few reports, but I guess that not many people do really. I think the ones that are sent will be of value, since at least they are adding to the database on drugs.

As already noted feedback, in the form of additional information or acknowledgement letters, was seen as the most important. He also provided a visible marker that their reports were important.

L1 Oh, I think they are valuable, apart from that Robin Ferner always writes a very thankful letter and he signs it himself, er yes.

R3 I do feel they are valued. There's clearly always a response back. I've never not got a response back, "thank you for filling this in" So that's good, that's a positive feedback, I'm comfortable with that.

I Do you feel that your reports are valued?

One regular reporter noted that he was unsure about the value of his reports, with data disappearing into a "black hole", and did not know if his personal performance in ADR reporting was adequate.

R1 *I don't know how I'm doing compared with other people anyway. I don't get any reward for it, in terms of feedback that you're doing a really good job, you know, or you're really crap. It, the data, disappears into a black whole, and as I say there is a competitive element to these things. Altruism only goes so far.*

Non-reporters had little understanding of the value of an individual Yellow Card report, but expected it must have some value because of the existence of the Yellow Card scheme.

6.9.10. Patient reporting of ADRs

Patient reporting was widely seen as a step forward by interviewees, with little active disagreement against its implementation – even if some were dismissive of its absolute value.

L4 *No, its probably very good thing. And they're not going to tell us; they stop their medicine and send in - send in the Yellow Card. No, I'm sure the more information you get, the better. And, as with everything in life, it's sifting out the validity of the information. It's like an Internet search isn't it? You don't know the authority of the particular site. The information overload can mask, you know, the whole thing.*

Some interviewees suggested benefits of patient reporting. Such as it could increase the number of ADRs reports made, give a more varied selection of ADRs, allow patients to take responsibility for reporting and their own health, and would also act as a therapeutic activity for patients who felt they had suffered an ADR.

L7 *I can't see any problem with it. It'd increase the volume and presumably the scatter of your results, but they potentially could be very valuable. I have no problem with it. It sounds like a good idea, actually.*

It was also seen as complimentary to GP reporting, with a suggestion that duplicate reports would add value. It was suggested that the scheme should be publicised within pharmacies.

Regular reporters and lapsed reporters expressed more concern about the extension of reporting to patients in comparison to non-reporters, with some suggesting it would be unreliable.

R5 *[laughter and pause] That's a bit useless isn't it? I mean the patient, that will be hampered by the fact that as soon as it's mentioned in the leaflet I'm sure that particular side effect goes up in patient reporting. Like people who have myalgias in statins, with statins for instance lots and lots of people come and say that they have muscle aches and pains with statins because they have read the leaflet and really the*

statins do not have any other side effects, all of them are old people, so if they have aches and pains and think a drug could be responsible then they usually blame it.

There was concern about the scheme being inundated with “chaff” without the filtering of suspected ADRs by a trained professional, leading to concerns about the sifting out of valid information and the effectiveness of the regulator to uncover drug safety signals.

R7 Possibly there may be some from the patient that are interesting and come out, but my experience of people reporting reactions to me is that people have a very funny idea of what a reaction is and what a drug might have done so I might have an awful lot of chaff and noise to the system.

GPs explained that a number of events that patients ascribe to drug therapy do not fit with their professional opinion. Some patients were considered susceptible to ADRs by suggestion – usually contained with Patient Information Leaflets. There was concern that the majority of the reports would be non-serious reports, reflecting the nature of the unfiltered patient reports that most interviewees described seeing, and concern that patients would not detect serious reactions. One example given by more than one reporting GP was myalgia with statins, which they see as well known and minor, but which they cited as a common reason for patients to attend consultations about a suspected drug-related event.

Some GPs saw difficulties in obtaining information from patients by use of a webpage or printed form. Concern was expressed that card can be difficult to fill in even when the patient is doing so with the GP is present, so it may be harder for them when on their own.

L10 I suppose they might be difficult to interpret, I don't know what the format of the reporting is, similar to the doctors scheme? I mean it can be quite difficult, even face-to-face trying to tease out drugs, whether what they are complaining about is related or not, so I imagine that reporting on a piece of card or a paper rather vague symptoms in a disorganised way can be quite difficult to interpret at the other end.

Another concern was that about the nature of the patients who would comprise the reporting population and fear that that it would be atypical in comparison to the general population.

N7 I would guess I would worry that our most vocal patients are the ones that would get the most adverse reactions, who are very cynical about all drugs and all interventions and look out for problems, I guess you might get a skewed view because of that, but I

guess that would be useful, because if you are picking them up from when doctors report, then you are just looking for trends, not just making a continuous link between a drug and some problem.

There were concerns about “oddball” reporting, pressure groups pushing particular agendas, and a concern that particular social classes or computer-literate individuals would be over represented.

R2 *Whether you may have people with their own baggage and prejudices actually reporting. It's a bit like NHS public meetings, because I'm still on the executive committee of the PCT, and I have chaired that committee for a number of years. In public meetings you tend to get the same people with the same issues raising them all the time, again. You don't tend to get the general public at these meetings, and I just wonder if there is a danger that you may get, if not pressure groups, individuals with their own baggage and personal issues, who tend to report rather than getting the ordinary guy, the man in the street. That's the one thing I wonder, if that perhaps might not give you a breadth of reporting, but only give you the oddball reporting.*

Those whose primary language was not English, or whose were less capable of expressing themselves were considered at a disadvantage. The more vocal patients were described as those more likely to be the more prejudiced against prescribed medicines.

Non-reporters appeared much more immediately supportive of patient reporting, expressing fewer detailed concerns about the nature of the data obtained and the ability of patients to report reactions, although concerns about objectivity were expressed. This could be indicative of a relative lack of knowledge about pharmacovigilance and their relative lack of interest in the scheme. Patient reporting was also seen as a way of increasing reporting that would not increase GP workload.

N3 *I didn't know that. A good idea. It will save us headaches and you might get better reporting.*

Interestingly, a small number of reporting GPs stated that a patient report might prevent them from reporting the same reaction, or that they might inform patient to report a concern themselves during a consultation. One regular reporting GP noted he had done just this, and would do so in future, unless the reaction was particularly traumatic in nature.

There was no active opposition to patient reporting, at worst some scepticism about its usefulness, largely borne out of their personal experience of patient reports of ADRs, much of which they considered unreliable or unimportant in nature.

6.9.11. Views on the Pharmaceutical Industry and the prescribing of new drugs

6.9.11.1. Therapeutic conservatism

Regular reporters did not generally consider themselves to be innovative prescribers, regarding themselves as therapeutically conservative with regard to the prescribing of new medicines. Past drug safety issues were used as examples of their therapeutic conservatism preventing the exposure of their patients to risks. There was a tendency of suspicion of claims about new medicines. Claims about the safety or efficacy of new medicines by drug representatives led to one GP ensuring that became “bloody minded” about finding ADRs.

R1 It's only better because its new. So there is a bit of me, you know a bit of bloody mindedness that says right you know I'm going to make sure that any reactions are reported. I think that the number of drugs, I think we over prescribe drugs and I think that we need in order to have a balance approach to drugs I do believe that we should be documenting the adverse reactions and the adverse effects of what they do.

Not all regular reporters considered themselves as therapeutically conservative, with two suggesting that they were more concerned with the evidence base, rather than immediate suspicion of new drugs. An example of complaints about a GP's high prescribing rate of statins was given, and how now the surgery appeared forward-looking for its early adoption of statins.

R10 Middle of the road, no I don't think so, not quite. It doesn't take a lot for me to feel confident about prescribing new drugs, assuming that the reports are sort of in the journals, that the people sort of recommending them are reputable. I think this practice has been lambasted for twenty years about our statin prescribing and now people are just about reaching our levels of statin prescribing, so yes I think I'm fairly non-conservative.

However, even in those cases there was scepticism about the claims of new therapeutic agents, some cynicism was noted about the marketing of new drugs.

Lapsed reporters similarly considered their prescribing to be therapeutically conservative. There was interest in evidence based medicine, and signs that attention was being paid to pharmaceutical advisors. Again some reporters raised examples of past drug safety issues or market withdrawals as reasons for avoiding newly launched drugs. Some reporters maintained a period of a few months before initiating prescriptions for new drugs – to see if any concerns are raised. Hospital-initiated prescribing was noted as a trigger for the prescribing of new drugs, as were the pharmaceutical representatives, who were described as “giving permission” for fellow GPs to prescribe new drugs.

L9 *I virtually never use a very new drug. I can't say I never use a new drug, because occasionally people are put on it by other doctors - hospital doctors. Yeah, then I would report anything that was unusual, but I'm not an innovative prescriber.*

Not all lapsed reporters were against the prescribing of new drugs. One, who noted the pressure not to prescribe new drugs, argued that good research showing benefits of the new drug, consultant use of drugs, and peer experience of a new drug might make him consider prescribing a drug. One GP considered the licensing process and drug development process as “rigorous” and argued there unless there was a safety issue, then there was no reason not to use a new drug. This GP noted that while he viewed himself as therapeutically conservative, his dispensary staff considered him the most likely to prescribe new medicines. However, he was interested in the presence of additional benefits in comparison to existing alternatives.

L4 *I think, yes, I - you do. I mean, I think there's - pressure on GPs not to prescribe medications until they've been tried and tested and peer reviewed and all the rest, but sometimes you get very good, I think, I might be wrong in calling it promotional material, but research on a new medication, say, for example Spiriva, which is just a long-acting Atrovent that where the improvement in the FEV1 one is maintained for a year and longer and you know it's expensive and if oh, yes, I think if there's that much benefit I'm going to try it before, you know, it's in common usage. We tend to wait until our consultants, specialists/colleagues in the hospital are sending patients out on it and obviously they're recommending it.*

[...]

I had no reason to suspect that it was an unsafe medication and while I was waiting for evidence that it was an unsafe medication, which it's not, I was depriving patients with very nasty condition to have because you feel you're slightly getting more short of breath and feeling suffocation.

This was a common theme with interviewees, prescribing of new drugs was either justified with reference to additional therapeutic benefits, or to situations in which therapeutic options were restricted by other factors.

Again past drug safety issues were cited as a reason for avoiding new drugs, and one GP gave an example of a patient dying after use of a new drug, which had made him realise the potential for harm with new agents

L8 Partly, it is part of my own personal character, partly just experience from things I may have seen in the past with drugs causing some unpleasant side effects before the doctors who prescribed them had enough information about the drugs to feel sure that he or she should have prescribed them. I can remember as a hospital doctor seeing a very unpleasant reaction to a new antidepressant, which had been on the market, this was back in the 1980s and the patient had died, died of DIC, disseminated intravascular anti-coagulation, and it was the first fatality from that particular drug - it wasn't long after that that drug was withdrawn from the market,

Once you have an experience like that it sort of imprints itself on your memory. Having seen people have nasty reactions to new drugs, in a way I'm ducking the issue, because maybe without being used you never actually get the sufficient numbers so you can judge on its safety, but from my perspective I am very cautious about new drugs.

If there is an over-riding reason for a new drug, over-riding, then I may prescribe it, but there has to be strong arguments for it.

Non-reporters also reported concerns about prescribing new drugs and viewed the time on market as an indicator of safety. As with reporting GPs, some interviewees noted that they had avoided problems with drug withdrawals by decisions to avoid prescribing newer drugs.

N5 Yes, I would be sort of watching and waiting with new drugs, because partly there is a sort of pendulum effect. When a new drug comes out, its fantastic and after a while it becomes a big doubtful, and then the penny sort of settles somewhere in the middle. But I guess that happens with most new products of any sort. I like to sort of wait for a while before putting somebody onto something brand new.

One GP avoided the use of new drugs, because he was aware that the prescribing of a newly marketed drug could generate Green Cards from the DSRU PEM scheme; he expressed annoyance at salaried GPs who attended his surgery who prescribed new drugs, but would not be responsible for the completion of Green Cards.

One non-reporter viewed new drugs as essential, and the reason that drug therapy progressed. This individual had a higher than normal trust of the pharmaceutical industry and was willing to try new drugs to obtain his own anecdotal experience.

6.9.11.2. Views on Industry

Regular reporters held sceptical views about the pharmaceutical industry, expressing awareness of industry failings with regard to drug safety, their promotional activities and marketing of diseases. An example of the latter was concern about the promotion of a drug for the treatment of restless leg syndrome after a question asking about his views on prescribing newly marketed medicines.

Some saw the Yellow Card scheme as standing in opposition to the drug industry, creating a non-promotional base of knowledge.

Despite demonstrating views that expressed cynicism towards the industry, some regular reporters noted that in their experience pharmaceutical companies were keen to learn about ADRs when made aware of them. One reporter noted that lowered reporting rates to the Yellow Card scheme could be attributed to doctors thinking companies were more careful with regard to drug safety, and that in comparison to the past it was harder to obtain product licences.

I Why do you think we have this decline in reporting?

R10 It must be because it is not perceived as important I suppose, and maybe we feel that the pharmaceutical companies are much more careful than they were 20-30 years ago so it is less likely.

I Do you feel they are?

R10 *I think, I think so, I think I think it is more difficult to get licences, or at least they have to provide more stringent evidence for safety and efficacy to get a licence than perhaps 20-30 years ago?*

Lapsed reporters pointed out the financial motivations and profits of pharmaceutical companies as reasons for treating claims about drugs with some scepticism. There was concern about the openness of the industry and suspicion of the material they produced in their promotional and scientific papers. Such concerns even extended to comparator drugs chosen in drugs trials. One common example raised was the issue of COX-II inhibitors. There was a clear preference for academic literature or other evidence based sources of information in comparison to industry provided information.

Industry was however viewed as a necessary evil in order to bring new drugs forward, however interviewees argued that prescribers should maintain the industry at “*arm’s length*”.

L5 *Some concerns really because they have obviously got profits to watch and we have heard about various companies maybe hushing up some of the lack of benefit of some of their products. You know, they will do a short-term study and the thing works, they do a longer term study and the benefit would be less pronounced, so the long-term study I understand wasn't published. So I do worry to a certain extent about their honesty. So, you know we have got to have a drug industry, otherwise we would never move forward, we know a nationalised system maybe like you had in the Eastern block before the wall came tumbling down. But that doesn't work.*

We do need to have private finance and you know a commercial market to make it with. But you have got to keep them at an arm's distance as well. Because you can't believe everything they say.

Non-reporters also viewed industry with a level of scepticism, but did expect genuine products of use to their patients. Although accepting of the need for industry, they were also aware of industry marketing. There was some evidence that non-reporters had increased trust of the industry with respect for large pharmaceutical companies’ reputation apparent. Trusted not to sell “*pond water*”.

I *Do you trust the pharmaceutical industry?*

N5 *Yes, with a degree of cynicism, but yes, I think they are not going to be selling us pond water, they will be producing genuine products that do what they are supposed to, or they should do.*

Another non-reporting GP, noting his early uptake of ACE inhibitors for the treatment of hypertension, for which he received criticism from the PCT prescribing advisor, said:

N3 *I and another doctor, we were the highest spenders on ACE, now they are telling us go for ACE. So I don't trust the government at all, I look at it like if the drug is out in front of me, it has come out on the market, it has to be a big company, it's a good company drug, yeah, I will try the drug.*

6.9.11.3. Views on pharmaceutical representatives

All groups of reporters had sceptical views of drug representatives, with the majority of regular reporters stating they did not see routinely meet them. Even positive stories of industry contact were tempered with a view that the industry was biased.

Most regular reporters did not routinely see pharmaceutical representatives, citing concerns about bias and trust. One regular reporter noted the effect pharmaceutical representatives had on his partner and the arrival of Green cards later.

R5 *Lots of times, yes. Usually from my partner, because my partner sees drug reps, and every time he sees a drug rep he fires off ten prescriptions of whatever, a new coxib or so and so, so he gets those further information requests back. If he's on holiday, then I have to do them all, if it is important.*

Those that did had a poor opinion of them, some choosing to press representatives on questions of evidence of safety or evidence, and citing the marketing materials as a motivation for reporting to the Yellow Card scheme.

R6 *Yes, and I don't like drug reps, I don't see drug reps. Because I think they give us very biased opinion about their product. And even if we think we are not being influenced by them, they wouldn't be employing drug reps if we weren't influenced by them. I have looked at the "No free lunch" website.*

Pharmaceutical representatives were viewed as poor sources of information both in terms of bias and because of poor training. Lapsed reporters were also not keen on pharmaceutical

representatives, unsure of what claims to believe and sceptical of promotional claims. They were perceived providing poor information and providing biased information.

R5 *I don't see reps, because I have the ambition to get my pharmacological information from other sources than people who are paid to sell me things. Drug reps aren't good enough. They don't have any biological background, I can't ask them questions that interest me or I can ask but they never know, they are not doctors or pharmacists, they are just people with any degree who had six weeks training in the new drug and showing me sort of slides - very nicely printed slides. So, I don't see the point, it's a waste of time. And thanks very much I can buy my own pens. I do actually, see here. [Interviewee holds out non-branded pen]*

Non-reporters did see pharmaceutical representatives, although there were comments noting more trust in local guidelines from PCT advisors. They viewed information from pharmaceutical representatives with “a pinch of salt”. There was a view that adverse effects were not routinely discussed. Even when pharmaceutical representatives were viewed as providing useful information, such as when providing further information from company medical information departments, there was still concern about data being skewed.

Interestingly two regular reporters to the scheme saw pharmaceutical representatives as potential advocates of the Yellow Card, even though one of them did not see drug representatives himself.

R5 *Yeah, instilling a moral sense of duty might work better, you know, like if you deal for instance with the pharmacological business, lots of people see drug reps, now I don't, but lots of people do. If the drugs reps went round and pushed it by the by, in an arrangement with the pharmaceutical industry that they mention the Yellow Card in each of their visits, that might work, if they said they were behind it and push it, they've got the push haven't they?*

6.9.11.4. Views on reporting to companies

Both regular and lapsed reporters gave a preference for reporting to the Yellow Card scheme, rather than directly to a pharmaceutical company. There was some concern about the nature of follow-up information requested by pharmaceutical companies. Concern was also expressed about the use to which reports would be put, if the data might be disadvantageous to them.

L7 *I wouldn't trust them to use it appropriately or I wouldn't trust them to use it if it was disadvantageous to them.*

L5 *I also do worry about in a certain sense how they handle information, whether they would just hush it up if it was something that didn't put them in a good light.*

In contrast interviewees described the use of the Yellow Card scheme putting data into the public realm, where users of products would benefit.

It would have been better to, or it was better to fill in a Yellow Card form, so it was out in the open, not with the company but with the users of the preparations.

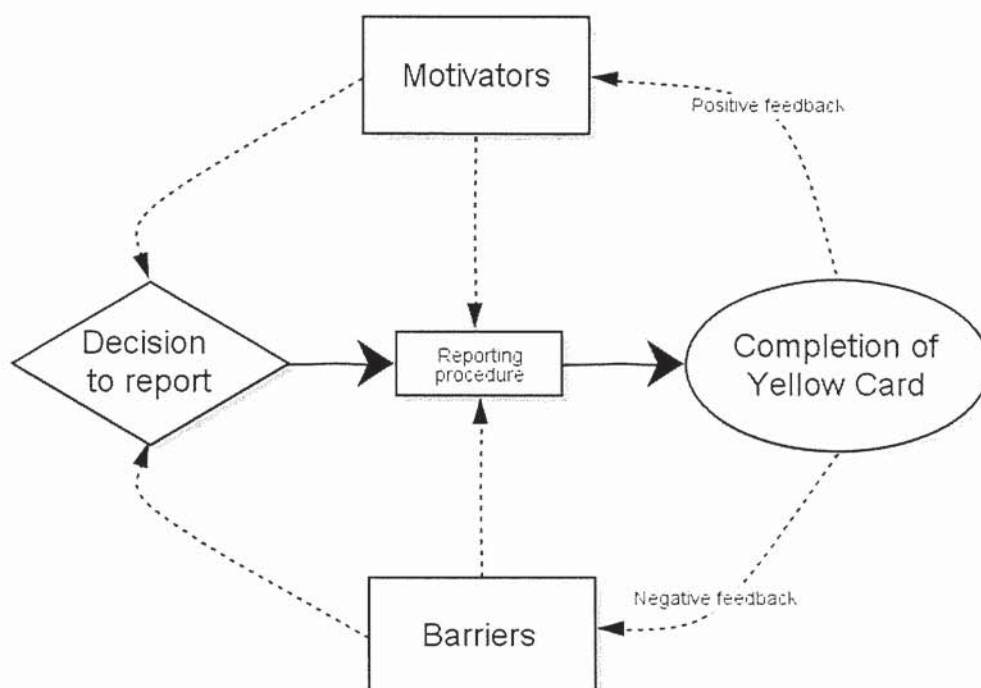
Those that considered they might report to a pharmaceutical directly still thought they should report in parallel to the Yellow Card scheme. Some reporters noted that they had made an ADR report to industry, because of mentioning an event to a pharmaceutical representative.

6.9.12. A theory of ADR reporting

The development of themes and memos during the analysis led to attempts to develop a theory for interaction between the various competing influences on ADR reporting in GPs. Figure 6-3 is an attempt to place the motivating factors and barriers to ADR reporting into the context of making an ADR report. Figure 6-1 and Figure 6-2 have already set up the conditions for the “Decision to report”. Detection of the ADR is a necessary, but not sufficient cause for the decision to report an ADR. Lack of awareness of ADRs, or confusion over the definition of what constitutes an ADR, will prevent consideration of ADR reporting. Knowledge of the Yellow Card scheme and its reporting criteria are not a guarantee for a decision to report either. As has already been described, GPs had their own criteria and judgements on the attributes of ADRs that warranted reporting, which are affected by their own personal experience and education concerned with ADRs.

Assuming the decision is made to report an ADR, there are a number of factors that influence the likelihood of a GP converting the suspected ADR into a Yellow Card.

Figure 6-3 : The influence of motivators and barriers to reporting adverse drug reaction



Central to the completion of a Yellow Card is the reporting procedure. The ease, or difficulty, of the reporting procedure affects the likelihood of completion of a Yellow Card. However, the perceptions and reporting habits of GPs are varied. Reliance on any one method of reporting is inadvisable, since some GPs may be adverse to use of an on-line reporting scheme, while others may not like paper-based systems. There was clear evidence of GPs using paper Yellow Cards as reminders to report, and the Yellow Cards in the BNF were viewed as a common source. Changes in the reporting procedure could also affect a GPs involvement in the scheme.

Barriers and motivations to reporting influence both the “decision to report” and “reporting procedure”. For example, if the Yellow Card scheme is not valued by a GP then they may not make the decision to report. On the other hand, a reporter may make the decision to report,

and then be not do so because of an inhibiting factor, such as a busy surgery, preventing the process of completing a Yellow Card.

Motivating factors are a complex mixture of personal values based on the reporter's view of the value of ADR reporting in their own practice and wider public health. Positive views of the Yellow Card scheme, and arguably some scepticism towards to the pharmaceutical industry, acted as positive motivation towards ADR reporting. Reporters' values such as a duty to report, guilt based on harm to patients and ownership of a reaction are also important positive drivers of ADR reporting. Altruistic motivations were also apparent, although in part there was also a view of obtaining benefits back from the Yellow Card scheme.

As discussed earlier, inhibitory factors also influence the decision to report and process of reporting. For example, for those that do make the decision to report, the influence of lack of time during the consultation, or other administrative pressures could lead to a Yellow Card not being submitted, even when the view of the GP was that a Yellow Card report should be made.

The model in Figure 6-3 also takes into account the importance of feedback, which can either augment motivating factors or barriers to reporting. Positive feedback can take the form of personal and immediate feedback to individuals (such as an acknowledgement of a Yellow Card report), or more generalised feedback (such as MHRA drug bulletins or regulatory action taken by the MHRA). Positive feedback may be re-enforcing of the personal habits and views of the reporter, creating a circle of virtuous reporting. Negative feedback could be based on disagreement with MHRA decisions or an absence of feedback. There is even the potential that supply of too much information could lead to negative views (such as the supply of large amounts of information in the form of a DAP) or requests for further follow-up.

It is important to note that this model does not make judgements on the relative importance of such factors, and it may be difficult to elucidate such values.

Non-reporters' interaction with the scheme is a mixture of the effects of ignorance of the scheme's value to drug safety and their views on the process. While they might be expected to have more inhibitory factors than a reporter, which this study does provide evidence for, it is also the case that there are non-reporters who never reach the decision to report, because of a lack of awareness of the potential of ADRs to exist and a lack of knowledge of the Yellow Card scheme.

6.9.13. General applicability of the ADR reporting theory

Although this conceptual model is based on the analysis of GP involvement in the Yellow Card scheme, it also provides a more general theory of involvement in the Yellow Card scheme for other professionals. However, the relative balance of the factors in the study will change dependent on the professional group involved, the environment they work within, and their educational experience.

6.9.14. Other models of ADR reporting

This study has confirmed the existence of some of Inman's "*Seven Sins*"²⁶². There was clear evidence for the sin of *Ignorance*, "I am unsure how to report an ADR", amongst non-reporting GPs, and even amongst some reporting GPs as to the type of reports the Yellow Card scheme encourages. *Lethargy*, "I am too busy to report", was also confirmed as inhibitor of reporting, as other studies have also confirmed²⁶⁵.

Other of Inman's "*Seven Sins*" were less prominent, such as *diffidence*, "I may appear foolish about reporting suspected ADR", *fear*, "I may expose myself to legal liability by reporting an ADR", and *ambition*, "I would rather collect cases and publish them". Legal liability was rarely raised in this study, and may reflect the long track record of confidentiality that the Yellow Card scheme has established. There may have been some

examples of diffidence, expressed as non-reporters expressing fears of not completing Yellow Cards correctly or in full, although this was commonly explained as a fear of provoking further work from follow-up letters from the MHRA. Ambition to collect a case series may be prominent in other reporting groups, such as younger medical staff in training posts within hospitals looking for publications, rather than the more established professionals interviewed in this study.

Complacency, “only safe drugs are marketed”, was primarily an issue in non-reporting GPs, with a positive view of the pharmaceutical industry

Inman proposed *guilt* as a sin, on the basis that there was an underlying reluctance of GPs to accept they had caused harm to a patient. It may be that this is a factor in some GPs’ failure to detect ADRs and a tendency to ascribe possible drug effects to other causes. However, in those GPs who did report to the Yellow Card scheme, guilt had the opposite effect to that proposed by Inman. Feelings of guilt led some GPs to develop an obligation to report a suspected ADR to the regulatory authorities. Sometimes this guilt was linked to reaction being reported, or sometimes to a more general concern about the level of prescribing and the risks associated with drug use. It would appear, on the basis of the present study, that guilt is a virtue rather than a sin.

Inman’s “*Seven Sins*” are therefore only a partial explanation for GP reporting within the present study, and ignore many other potential factors that may influence ADR reporting. Inman himself recognised that his criteria were based on theoretical views at a particular time²⁶⁶. Studies of doctors’ attitudes towards ADR reporting have shown varying degrees of importance ascribed to Inman’s “*Seven Sins*”^{264,265,268-270,272,274-277,279,280,368,369}. Additionally, Inman’s “*Seven Sins*” are entirely focused on negative factors related to ADR reporting. As the present study shows a number of motivating factors exist that may aid ADR reporting in

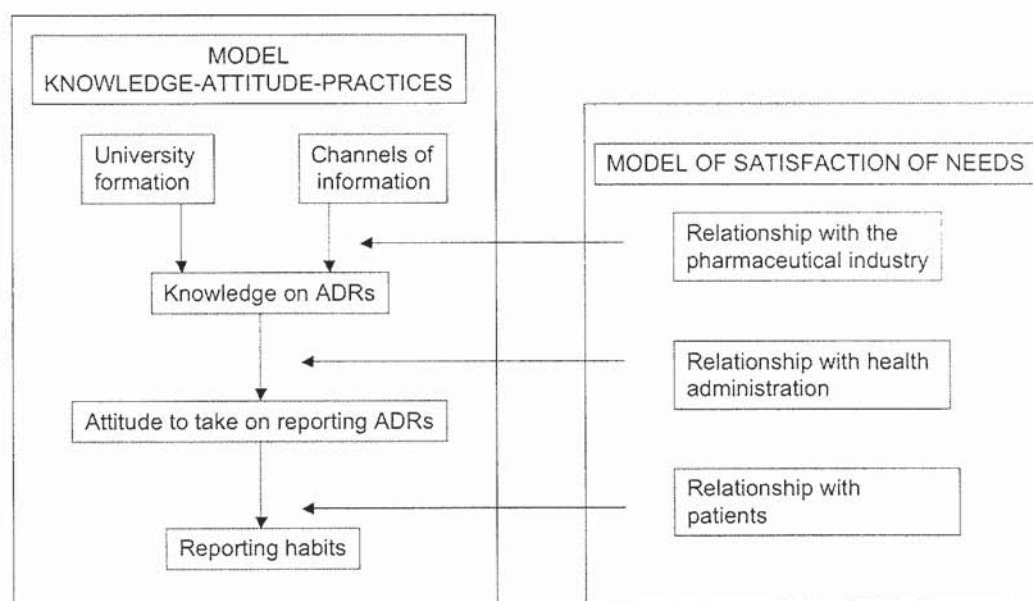
GPs, and therefore potential interventions to improve ADR reporting rates need to focus both motivators and inhibitors of ADR reporting.

Herdeiro et al³⁷⁰, have suggested a broader theoretical model of reporting of ADRs centralized on the medical professional, which considers ADR reporting as a habit. The habit is formed by development of the doctor's views on ADR reporting, and his interaction with the environment. The model distinguished between two major condition types:

- **The intrinsic condition** – related to the formation of the health professionals;
- **The extrinsic condition** – related to the all the factors associated with the professional interaction with the work environment.

The model is depicted in Figure 6-4

Figure 6-4 : Herdeiro's theoretical model of factors that condition health professionals' attitudes in the reporting of ADRs to medicines³⁷⁰



In Herdeiro's model, the educational formation of the doctor and sources of information about ADRs condition the professional towards increased vigilance towards ADRs. This knowledge generates the doctor's attitudes towards the reporting system, which in turn

generates the reporting practices of the doctor. This is known as the *knowledge-attitudes-practice* theory of acquisition of habits. Herdeiro's model recognises that the same inputs into the system would not necessarily lead to the same reporting habits.

The intrinsic system, is also modifiable by the pressure of extrinsic factors, whose influence can be explained by the *satisfaction of needs*. According to the *satisfaction of needs* model a professional will attempt to keep a harmonious relationship with their work environment, adapting consciously and unconsciously their practices to extrinsic factors. Therefore while it may be possible to change the level of knowledge and attitudes towards ADR reporting, doctors need to balance these external factors.

The model put forward by Herdeiro is persuasive, and the present study's findings appear to support the adoption of this model as a way of analysing the problem of under-reporting, and how to improve ADR reporting rates.

The relationships with the three extrinsic factors Herdeiro proposed are clear within the present study, where time with patients and views on patients' concern were apparent in the decision to report, and attitudes to the pharmaceutical industry and the Yellow Card scheme were also varied. The extent to which these intrinsic and extrinsic factors combine and interact will affect the probability of an ADR report being submitted to a regulatory agency.

6.9.15. Definitions, awareness and experience

This study has discovered confusion over the definition of what constitutes an ADR. Robins' et al²⁷² found that over half of doctors excluded well-known and well-established side effects as ADRs. This study found some GPs making a distinction between ADRs they viewed as predictable known reactions, sometimes called "side effects", and unpredictable ADRs, which they would view as ADRs. This even included such reactions as haemorrhage associated with warfarin.

An element of error in an ADR also led some to believe any adverse effect was not an ADR, since the adverse effects were caused by operator error rather than the drugs intrinsic properties. However, the past record of drug safety shows many examples of where an element of error is important in a suspected ADR, such as the prescribing of bupropion in those with pre-disposing factors for epilepsy despite warnings not to³⁷¹, the prescribing of cisparide in those with taking known interacting drugs³⁷², and the prescribing of methotrexate on a once daily basis³⁷³. Although there is a debate to be had about when a suspected adverse effect of a drug should be reported to the National Patient Safety Agency, or the Yellow Card scheme, the message should be given to reporters that the presence of an element of error is not a bar to reporting to the Yellow Card scheme.

6.9.16. Criteria for reporting

This study has confirmed some previously well-documented preferences towards reporting ADRs. Novel ADRs, serious ADRs, and ADRs associated with new drugs were preferentially reported over less serious ADRs, known ADRs, and ADRs associated with well-known drugs. In this study there was little evidence that reporters reported only ADRs that already had been found. Indeed, some chose not to report ADRs because they were listed in the BNF, and were therefore known.

Some reporters would look for high levels of plausibility of a reaction, while the Yellow Card scheme asks for mere suspicions. Temporal associations were valued more than pharmacological explanations. One of the weaknesses of the scheme is that filtering of suspected reactions can occur, with a potential loss of important drug safety signals. A case study is that of practolol, where after a letter to the BMJ the CSM were inundated with ADR reports that had previously not been associated with the drug. Education needs to clarify that only mere suspicions are required to report an ADR.

The present study also highlights the continued problem of under-reporting of serious well-known reactions. An example of this is warfarin haemorrhage, which continues to be major cause of fatal ADRs in the UK³⁷⁴. This is not purely because the reaction is known to occur with warfarin, but because it is pharmacologically predictable.

However, despite these differences between personal reporting criteria and MHRA reporting criteria, the main reporting criteria of reporters was generally in line with MHRA criteria. Reporters created their own pragmatic criteria based on their experiences and consideration of what they considered of value to the yellow scheme. It is arguable that while effort should be expended on promoting awareness of the scheme, educating reporters who already report to the scheme about the criteria for reporting may be counter-productive.

Re-challenge was not noted by reporting GPs, but two non-reporters did advocate its use. Reporters were more interested in the dechallenge following the withdrawal of a drug. Cessation of the suspected ADR was noted as making an ADR report more likely.

In contrast to questionnaire studies of ADR reporting that have been performed, the present study noted the effects of a patient's views on the likelihood of a GP reporting a suspected ADR report. Patients' views of a suspected ADR report could influence a GP to report a reaction. However, these views could be over-ridden by the views of the GP on the plausibility of the suspected ADR. Although strong views of a patient could increase the likelihood of a report, there were also descriptions of patients who would not be taken seriously by the GP because they were perceived as "*whingers*".

The limited awareness of increased vigilance for paediatric reactions and lack of awareness that the Yellow Card scheme accepted reports concerning herbal preparations is of some concern.

Knowledge of the black triangle scheme was good, however reporters noted that they had to check the BNF for the black triangle status of a drug. Computer systems do not flag black triangle status when GPs are prescribing. The MHRA may wish to contact GP prescribing system developers to see if alerts could be added to such systems.

6.9.17. Awareness of the scheme

The present study showed that awareness of the scheme came from a variety of sources including undergraduate education, post graduate education, and the BNF. Some of the reporting doctors had obtained their attitudes and view of spontaneous reporting as an important activity from their training, and this may have led to their valuation of ADR reporting as important. This would underline the importance of teaching about ADRs at the undergraduate level.

It is important to note that education did not always predict participation in the ADR scheme, with some non-reporting GPs aware of being taught about the Yellow Card scheme.

Awareness of the Yellow Card scheme is necessary for a report to be made. However, non-reporters' behaviour cannot be explained purely because of a lack of knowledge of the scheme, since many were aware of the scheme. Lack of practical use appeared more important.

6.9.18. The BNF

The BNF plays a number of important roles in awareness of the Yellow Card scheme. Those who had not been formally taught about the scheme often discovered it in the BNF. It is important that the BNF continues to include information about the Yellow Card scheme and Yellow Cards. Provision of Yellow Cards in the BNF was credited with rises in reporting rates¹⁵⁸. The BNF is a credible and trusted source, and there is some evidence that the Yellow Card benefits from the association in the present study.

Since March 2006, the Yellow Card scheme has been given less space on the back of the BNF. Since 1998 there have been increasing amounts of additional material placed in the back of the BNF (such cardiovascular risk tables) moving the Yellow Cards away from the more prominent back page position.

Consideration should be given to placing the current bright yellow strip on the back of the BNF, on the front cover of the BNF.

The BNF also played another role in the reporting of suspected ADRs, with reporters using the BNF to refute or confirm an ADR, some times choosing not to report if the ADR was not present. In addition, the use of the term “side effect” by the BNF leads some reporters to discount reportable ADRs as side effects, and not report. Use of the term ADR in the BNF’s drug monographs would help reduce confusion.

6.9.19. The reporting habit

An important insight into ADR reporting found by this study is the development of reporting habits by GPs. Regular reporters developed habits of practice that became self-reinforcing. Although training cannot directly induce the development of such habits, they are of importance because they do suggest that actions that can help re-enforce this habit or disrupt it are of importance.

The temporal relationship between discovery of an ADR and completion of a Yellow Card was perceived as crucially important. Changes in the practice environment can damage the opportunity for such reports to be made, which are often made in moments of opportunity that GPs find during the day or at the end of surgery.

Therefore, the availability of Yellow Cards is crucially important. Loss of the Yellow Card from the BNF could lead to major losses in reporting, as would reliance on an electronic Yellow Card. Care must be taken not to impinge on the reporting habits of GPs.

6.9.20. The Yellow Card

As the Yellow Card was not seen as particularly difficult to complete, major changes to the Yellow Card are probably not necessary. However, the comment about the tick boxes on the card about serious or life-threatening events from one reporter is worth considering. The tick boxes were introduced to make completion of the card easier for the reporter, and presumably to enable the MHRA to judge if a reaction is serious or not. However, reporter views about what is serious appeared to differ from that of the MHRA, and reactions will be coded at the MHRA as serious or not using their own criteria. It is therefore worth considering if the tick boxes should be removed or not.

The comments from Yellow Card reporters about the Green Card should also be borne in mind, any increase in the size or the complexity of the Yellow is likely to be resisted by reporters and potential reporters, and could lead to some deciding not to report.

Electronic reporting was not favoured by many reporters to the scheme, even by computer literate GPs, who saw the paper card as easier to fill in. An automated Yellow card which populated fields from the GP's patient information system would however be widely welcomed.

6.9.21. The changing practice environment of GPs

This study found that GPs thought their working day was becoming more pressurised, with less opportunities for non-priority tasks within normal working hours. Although not all reporters felt this was reducing their ability to report, there were examples of GPs changing their reporting habits due to work pressures.

As well as increasing pressure on the working day, there are changes in working practice. The move to paperless offices means that work can no longer be taken home, pushing administrative tasks into the GP's working day. Even though practices are setting up at-home

access to computer systems, it does not necessarily mean that old habits, such as working in front of the television, would resume to the same extent.

Administrative pressures have increased on GPs in recent years, although may have been preceded by earlier changes related to the internal market established in 1991. Pressures seem to vary depending on the practice of the individual GP, and the use of administrative and managerial staff. Changes related to the new GP contract also appeared to be putting pressures on GPs within consultations, leading to reduced opportunities to report and an increasing number of tasks the GP had to focus on within the consultation. Incentives were seen to be driving GP activity towards QOF related activities; which may be affecting the attention paid to other areas not subject to incentives, such as Yellow Card reporting.

6.9.22. Barriers to reporting ADRs

The present study has described a series of barriers to Yellow Card reporting. Lack of time has been described as a barrier to reporting by many and the present study confirms lack of time as an issue. Within UK general practice, there is a perception of increasing time pressures, as well as changing levels of administrative and working practices. Pressure within the consultation as a result of the new GP contract may be increasing the number of tasks to be performed by the GP within a consultation, pushing Yellow Card reporting out of the consultation, and damaging reporting habits of existing reporters.

Fear of medico-legal concerns was not confirmed by the present study, which fits with other published studies.

6.9.23. Motivators for reporting

The present study's discovery of positive motivators for reporting to the Yellow Card scheme are in contrast to other UK studies that have focused on inhibitors of ADR reporting. Motivation to take part in the Yellow Card scheme is arguably of more importance than inhibiting factors. Even with no inhibitors, a lack of motivation to report will prevent a

report. A key finding was the strength of feeling that reporting to the Yellow Card scheme was a duty. While previous studies on ADR reporting attitudes have asked about professional obligations and duty, the qualitative nature of this study demonstrated that such beliefs were more deep-rooted than simple statements about professional obligations. The issue of duty was personal and part of the individual's moral perspective on the scheme or valuing of the scheme in providing a public service.

As already discussed, a surprising theme was that guilt was a motivating factor, running counter to Inman's suggestion that guilt would be a barrier to reporting.

6.9.24. Financial incentives for reporting: knights or knaves?

One proposed mechanism for increasing the number of Yellow Card reports submitted is the issue of financial incentives in the form of targets similar to those in the Quality of Service Frameworks (QOF) used by GPs or by individual payments for each yellow card²⁸⁹. The present study showed revealed a paradox within GPs' views about such financial incentives. While many did not think such incentives would affect their reporting rate, they did think they would affect other GPs. There was an awareness that the culture in general practice was changing, with a move from a primarily professional attitude towards a more financially driven behaviour:

L7 They want to improve, and they'll have their targets to whatever point, and certainly the culture's changing from doing things as part of your role to, "I'll do it if I get paid, but I won't otherwise." That is QOF is if it's paid, they'll do it. If it's not paid, well find someone else to do it.

A non-reporting GP, who was deliberately caricaturing some of his professional colleagues, said:

N3 For heaven's sake kid, you can't get anything for free. You've got to support a family. You've got children, you've got kids, you've got a mortgage to pay, and I'm running through angina, through stress, to get my QOF points, to get my money. And you tell me in the end there is no money, I'm not Mother Theresa, I don't have wings. I don't have Tony Blair's halo on my head.

However, many existing reporters had concerns about the introduction of a fee or target for Yellow Card reporting to the Yellow Card scheme. One concern was that “*loose reporting*” would occur, creating “*chaff*” in the MHRA’s database. Although there have been examinations of the effect of a fee on reporting rates, it is not known what the effects of a fee would have on the balance of the type of reactions reported. Even if a financial incentive did introduce “*chaff*” into a system, that might be of limited concern, since signal detection methods depend on “*ordinary*” reactions to be reported, as well as the more novel, in order to allow any potential signals stand out from the database¹³². However, if such reports were received as a replacement to existing ADR reports from interested and astute ADR reporters, then the nature of the database could change.

A parallel can be drawn with the work of Richard Titmus, a sociologist, who examined blood donation programmes in his most famous piece of work, *The Gift Relationship*³⁷⁵. Examining the UK blood donation service, and a variety of international blood donation systems, Titmus concluded that the introduction of paid blood donations “crowded-out” altruistic motivations and lost donors who were not donors for financial reasons. In addition the quality of blood supplies fell in paid donor systems, as those who were motivated by financial motivations replaced those motivated by altruistic reasons. He described the donation of blood for no fee as a social gift, or form of creative altruism, which allowed an individual to express themselves, and enrich life for anonymous others. He argued that a private market in blood limited the choice of individuals; one of those choices being to have a “*Right to Give*” and to develop “*fellowship relationships*” in society. The UK’s National Blood Transfusion Service was described as an example of how “*such relationships between free and equal individuals may be facilitated and encouraged by certain instruments of social policy.*” Providing payment denied an individual the right to enter into a gift relationship. It is arguable that the Yellow Card scheme acts in a similar manner to that of the National Blood

Transfusion Service, with a yellow card equivalent to a blood donation. Altruism and duty figured highly in Titmus's qualitative work on blood donations, one research participant said:

I am a father of two, and feel that if I, or if any of mine ever need blood, they have a moral right to it. It is an obligation of a father

While differing systems, parallels can be drawn with the views of reporting GPs in this study in relation to a sense of duty or altruism; Titmus was unsure of the distinction between altruism and duty in many cases.

L8 *I can't imagine a doctor that prescribes, not being interested in reporting. To me that seems incredible,*

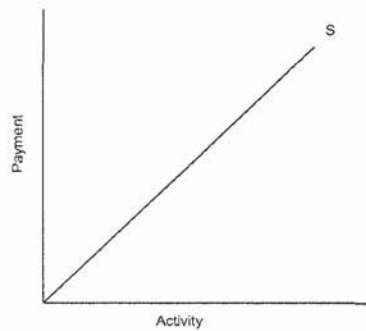
Indeed, there were examples of GPs suggesting that a fee would de-motivate them or reduce credibility in the Yellow Card scheme, by changing the nature of the scheme. Similarly targets that included a fee were seen as political in nature, moving the emphasis away from their interest, self-motivation and ownership of suspected reactions towards meeting someone else's targets and views.

Le Grand in *Motivation, Agency, and Public Policy: Of Knights & Knaves, Pawns and Queens*³⁷⁶ described ways of creating public policies to appeal to two instincts within public employed in the public sector. Firstly policies that viewed people as motivated primarily by self-interest, knaves, and secondarily, those who are predominately motivated public-spirited or altruistic notions, knights.

As an example he discusses an altruistic activity that confers a benefit on others, but requires the individual undertaking the activity to incur a personal cost. Such a description fits the current version of the Yellow Card scheme.

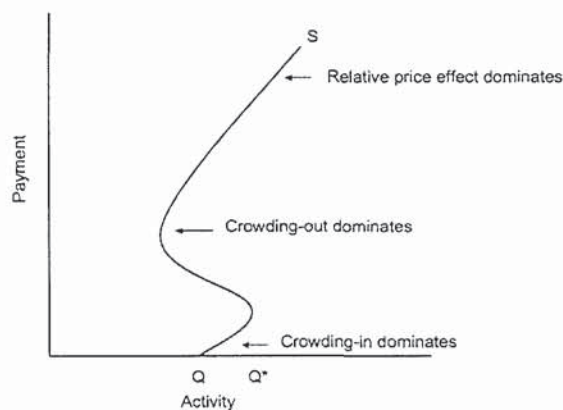
If all individuals are all considered to be knaves, deriving no benefit from the activity concerned, then payment will be required to motivate them to undertake the activity. The more money given, the more activity is produced (Figure 6-5).

Figure 6-5 : Knavish Supply (From Le Grand, 2003)³⁷⁶



In the case of knights a different picture is produced. Knights derive some intrinsic reward from the activity undertaken, without the need for a payment. Figure 6-6 explains depicts the relationship between payments and knightly activity.

Figure 6-6 : Knightly Supply (From Le Grand, 2003)³⁷⁶



Individuals will perform a certain level of activity, Q , without payment. A small payment may be viewed as recognition or acknowledgement of their sacrifice and they may become more favourable disposed towards the activity, moving activity to Q^* . However, if payments are further increased the level of sacrifice begins to fall, reducing the intrinsic reward they obtain from the activity. Supply is reduced and a “crowding-out” effect begins to dominate. Supply can even be reduced to that below the original activity level produced from no payment. As payment further increases the relative price effect dominates and supply will increase again.

Examples of financial incentives having perverse outcomes are common and accepted by economists. Some have argued that the use of financial incentives in public sector reform is dangerous, because such reforms can weaken the knightly motives of public servants such as doctors and teachers³⁷⁷. The present study does appear to provide some evidence that knightly motives exists in current reporters to the Yellow Card scheme.

A number of changes in general practice over the past 15 years may have already eroded the knightly motivations of GPs, and could perhaps have eroded support for the Yellow Card scheme. Firstly, an internal market was introduced to primary care in 1991 by then conservative government, producing fund-holding GPs. By 1997 over half GPs were fund-holders. It is noticeable that the peak of reporting to the Yellow Card scheme occurred in 1992, and a gradual decline was perceived during the 1990s¹⁷. The extension of the Yellow Card scheme to other reporting groups from 1997 to 2002 was an attempt to stem this fall, but GP reporting has continued to fall. Even though the internal market was removed in 1997 by the Labour administration, primary care continued some form of incentive structure. The 2004 GP contract moved GPs towards an even more direct incentive structure, which has arguable further undermined knightly behaviour. While this gradual reduction in altruistic motivations may not be the whole story, it may explain some of the decline in Yellow Card reporting since the high point of 1992.

There are also fears about the death of medical professionalism. While a sense of professionalism has been a motivating factor in the past, shifts in the doctor-patient relationship have occurred. Rather than ethical obligations, targets have become important³⁷⁸.

It is noticeable that the studies examining payments tended to use small fees that probably are not of the level to dissuade people from reporting, but were big enough to create some increase in activity. For example, a Finish hospital study obtained a 53% increase in ADR reporting activity when reporters were given free desserts at the hospital cafeteria³⁷⁹. Nita et

al found that 13% of Australian hospitals running monitoring schemes for ADRs that gave small rewards such as chocolate, ADR pens, letters and movie tickets had higher ADR reporting rates. One high reporting hospital provided a three monthly prize for ADR reporting. Even the effects of Feeley's widely cited study looking at the use of a fee³⁸⁰, could be explained by the increased interest being paid to ADR reporting, rather than the fee itself as there was no control group. Other studies have seen no noticeable improvements with small fees¹²⁹.

Currently the evidence for introducing a fee or financial target to Yellow Card reporting is limited, but there are potential dangers. The fee that would produce an optimal level of activity is not known. Of more concern is that financial target could be counterproductive, and not just to GP ADR reporting rates. A fee given to GPs would also alter the perceptions and attitudes of other professional groups, who are still building their reporting culture towards the Yellow Card scheme.

6.9.25. Feedback from the MHRA

The present study has shown that feedback that reporters obtain is of importance. Feedback encourages reporters, confirms they were to report a reaction, and creates an automatic reminder. Feedback creates a virtuous circle of activity. Even a simple acknowledgement letter of the Yellow Card report being received by the MHRA may be perceived by the reporter as an intrinsic reward for participation in the scheme.

Therefore communications with reporters are a marketing and educational opportunity. Feedback should be prompt and accurate. The present study found that personal contact helped to strengthen relationships of GPs with the Yellow Card scheme. Local feedback to Yellow Cards was valued. At the moment there are anecdotal reports of delayed acknowledgement letters within the West Midlands, supplied centrally from the MHRA, along with incorrectly spelt names of reporters. Even though interviewees were largely

unconcerned about submission of Yellow Cards to a central location, local feedback was valued. A mechanism that continued to allow local YCCs to communicate with their reporting base would prevent such relationships eroding.

The MHRA should also consider changes to the form of the aggregated data supplied when the tick box asking for further information is used on the Yellow Card. Although the provision of DAPS on the MHRA website should continue, they are seen as too large and complex when received as feedback. One way forward would be to adopt Mann's suggestion of producing mathematically ranked data, rather than system organ class ranked data³³. Even though such information would still be subject to the same caveats concerning interpretation that DAPs are subject to, if kept within a manageable size they could improve the value reporters place on the information, and hence their valuation of the Yellow Card scheme.

There were no real concerns about being approached by the MHRA for follow-up information about reports. In comparison to requests for follow-up information from industry (which was perceived as intrusive), the MHRA requests were viewed as further confirmation that their report was valued.

6.9.26. The MHRA

The role of the MHRA was not well known to reporters, a finding also found in the recent market research commission by the MHRA³⁸¹. It was confused with a number of other government agencies, including NICE, and non-government agencies like the DSRU. Little knowledge of other parts of the MHRA was apparent. The CHM was not widely known, although the CSM was. It is arguable that the MHRA gave up a valuable "brand" with the 2005 change from the CSM to the CHM. The CSM also had the benefit of the word "Safety" being in its title.

Further name changes should be avoided, especially with regard to the Yellow Card scheme, which was known about by all interviewees.

The Yellow Card scheme was seen as a mechanism for GPs to help create independent information. This was apparent even in individuals who distrusted central government on other health issues. Reporters considered independence from the industry important. It is therefore important that the MHRA continue to be seen as distinct from the pharmaceutical industry. Some have argued that for that reason, the licensing and drug safety surveillance activities of the MHRA should be split. However, signs of this debate were not apparent in GP attitudes.

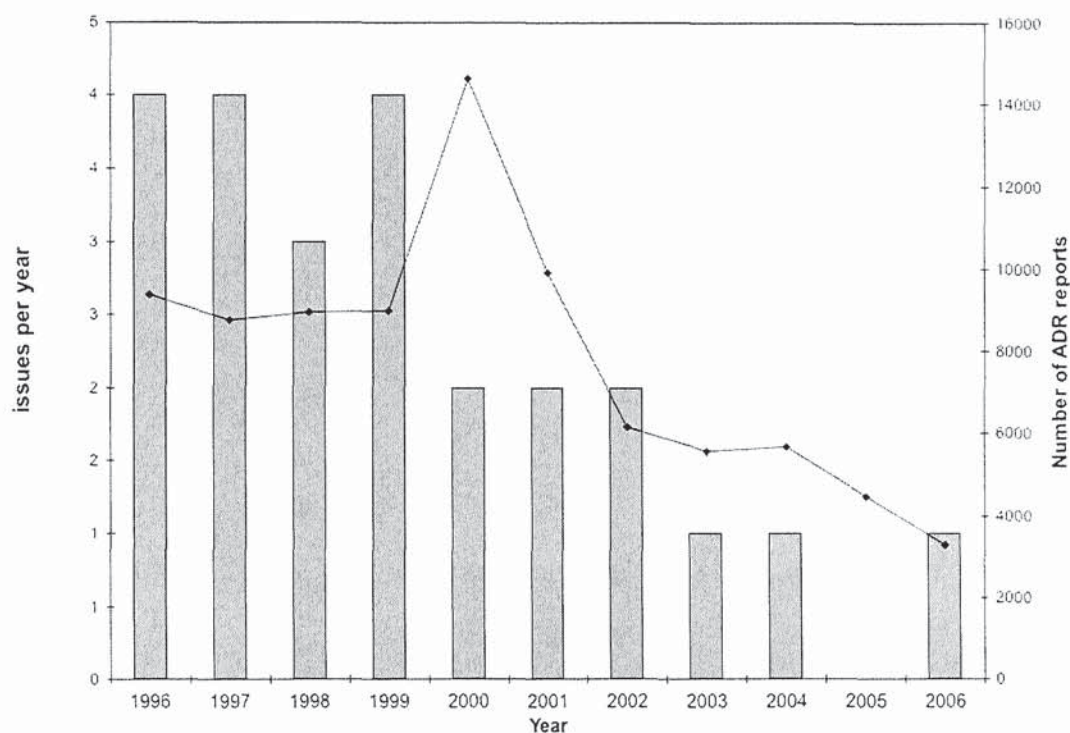
The MHRA should consider regulatory action taken on matters of drug safety as potential marketing opportunities. Recently drug safety issues such as rofecoxib and rosiglitazone have led to criticisms of the Yellow Card scheme, and the potential for reporters to come to the conclusion that the Yellow Card scheme is not effective. However spontaneous reporting is still crucial in drug safety, and previous drug scares (such as benoxaprofen and practolol) led to rises in ADR reporting. It is therefore of importance that positive stories of the effectiveness of the Yellow Card scheme are widely covered; much of the current focus is either on under-reporting, or ADRs that could only be discovered in trials.

The MHRA's *Current Problems in Pharmacovigilance* was valued by reporters, and viewed as a source of independent information. It was compared, and confused, favourably with *The Drug And Therapeutics Bulletin*. The paper format of the bulletin was liked, with many reporters complaining about the lack of non-promotional printed materials. In the past few years *Current Problems in Pharmacovigilance* has been published infrequently (**Figure 6-7**).

While it is simplistic to suggest that the entire decline in GP reporting over that period is due to a failure to publish *Current Problems in Pharmacovigilance*, it was a key marketing tool credited with increasing reporting rates in the past^{158,286}.

Figure 6-7 : General Practitioners' Yellow Card reports 1996-2006 and number of issues of Current Problems in Pharmacovigilance per year

I



A new safety bulletin, *Drug Safety News*, was launched by the MHRA in August 2007. However, it is an electronic document, which loses one of the key points cited in its favour by GPs in the present study. Additionally, Current Problems, like the CSM, was a well recognised “brand” associated with the Yellow Card scheme. Although the MHRA are now committed to a regular monthly publication, it remains to be seen what the impact of the new bulletin will have on ADR reporting rates.

Drug alerts were now perceived as much more timely, although there was concern about the formatting of emails. Emails were considered too long; taking too long to get to the central point. In addition GPs thought they were receiving a lot of emails not of direct relevance to their practice, possibly diluting the message. Despite improvements in the alert system, GPs

still were annoyed by the tendency of the media to break stories about drug safety. However, there was an view that this was out of the control of the MHRA.

Interviewees were generally supportive of the MHRA's regulatory decisions, even though some decisions (notably that concerning co-proxamol) were considered to have created work for GPs.

The MHRA's Yellow Card centre was viewed favourably. However it should be noted that this analysis was performed by a member of staff from the YCC, and the GPs were aware of the nature of the reporter. However, a number of reporting GPs brought up spontaneously specific instances of the centre's staff contacting or speaking to them, and there did seem to a value placed on having a local YCC.

6.9.27. Counterbalancing the industry

Interestingly, reporters to the Yellow Card scheme in this study appeared to be conservative prescribers, with suspicions of claims about new medicines. They were also wary of drug representatives, and generally distrustful of the pharmaceutical industry. Although they were the higher reporters to the West Midlands region, they suggested they avoided prescribing new drugs to avoid unknown safety issues. This is paradoxical given that they are the ones more likely to report the unknown reactions the Yellow Card scheme is meant to detect. However this would appear to confirm the findings of the retrospective review of primary care ADR reporting in Chapter 5. Those that did prescribe new drugs early, were influenced by other colleagues, and consultant adoption of new drugs, which matches other research into adoption of new drugs³⁸².

Interviewees were generally sceptical of the pharmaceutical industry, especially with regard to drug safety claims, but did expect them to market products that were beneficial. Past drug controversies, like COX-II, were cited as failures of the industry. There was also widespread mistrust of the information the industry provided from drug representatives, and reporting the

industry was greeted with scepticism by some reporters who were unsure that the industry would do anything with them. Non-reporters were generally less sceptical towards the industry. It may be that Yellow Card reporting is performed by people who are generally sceptical towards the industry.

6.9.28. GPs' views on patient reporting of ADRs

GPs were supportive of patient reporting of ADRs. Despite concerns about the validity patient reporting expressed by some interviewees there was no actual antagonism towards the patient reporting scheme, even though it could potentially lead to reports concerning their prescribing. There is a potential for some GPs to direct patients to complete ADR reports rather than completing themselves.

6.9.29. Strengths and weakness of this study

One weakness of the study is that there may not have been sufficient difference between the lapsed reporters and regular reporters, however examples were found of broken habits. People may also have said what they were expected to say – although reporters to the scheme did acknowledge failings and we did have knowledge of their actual performance. Set nature of the participants could not look for alternate cases – although there was some diversity within the GPs found.

The researcher's "*badging*" as part of the West Midlands YCC may have led bias in recruitment, as well as effecting participants' behaviour within interviews. It is possible that the background of the researcher and perceptions of his organisation could have had either a negative or positive effect on recruitment. The variation in recruitment rates for the three groups of reporters may reflect this.

GP awareness of the researcher's professional background may also have influenced their views, and may have led to "*politically correct*" answers being provided.

Although the purposive sampling method chosen did lead to a wide variety of reporters' views being sampled, later stages of recruitment of non-reporting GPs was difficult, leading to a decision to change to convenience sample from contacts found during the study or via professionals connections. However, since this sampling is in-line with the theoretical considerations about validity based on a grounded theory approach, it was not considered that this had led to bias within the study. The difficulty in recruiting non-reporting GPs is perhaps unsurprising, however it is of interest that lapsed reporters to the scheme were far more willing participants than regular reporters, possibly indicating guilt that they had given lowered priority to Yellow Card reporting in recent months.

A strict definition of grounded theory means that the researcher is naive to the research area, and developed an understanding of the data based on the themes within the data. However, this ideal was impossible to meet. As far as possible the researcher attempted to minimise the effects of his previous exposure to research on doctors attitudes to spontaneous reporting and his professional involvement and prejudices related to the Yellow Card scheme. However, readers of this study should be cognisant of the perspective the researcher may have brought to the study and any systemic bias that may have arisen throughout the coding process, memo-writing and theory generation.

However, the use of coding allowed some attempt at a uniform approach, although the researcher was aware that his internal views and biases could have effected his coding of the data. The independently analysis of transcripts by a second coder did provide confidence that the researcher had remained open to emergent themes within the data, with the same key areas arising through independent analysis.

The theoretical basis for ADR reporting is grounded in the views of GPs, and their interaction with the Yellow Card scheme. However, its generalizability is open to question. There may

be other influences on GPs, and the relative value of particular influences cannot be measured.

Although further research is needed to, perhaps of a quantitative nature to discover the fit of the theory against the broader population of GPs, the researcher believes that the process of coding and constant comparison between subjects led to an acceptable level of validity within the study.

6.10. Summary

The present study has provided a valuable insight in to the interaction of GPs with the Yellow Card scheme. A theoretical framework for ADR reporting has been developed for GP ADR reporting, which may be applicable to other reporting groups. Positive motivators for reporting are of equal importance to Yellow Card reporting. Yellow Card reporting is strongly motivated by altruism and duty, and there is resistance to the idea of a financial motivation.

Chapter 7 General discussion and conclusions

7.1. Discussion

This thesis has examined issues related to the spontaneous reporting of reporting of ADRs within the UK. Major emphasis has been placed on the relationship between the GP and the Yellow Card scheme. Since the formation of the Yellow Card scheme in 1964, the GP has played a major role in the reporting of ADRs in the United Kingdom. However, in recent years, as Chapter 5 of this thesis demonstrates, GP rates of ADR reporting have fallen significantly in absolute terms.

The qualitative study of GP attitudes towards ADR reporting in Chapter 6 was undertaken in to explore reasons for the fall in ADR reporting rates, and to examine differences between non-reporters and reporters to the scheme. Lapsed reporters were also examined. It was found that ADR reporting is governed by a complex interaction of knowledge, values, and motivations that lead to the decision to report and a following act of reporting. Inhibitors of ADR reporting were also discovered and confirmed, such as lack of time and changes in working practices. It was found that some of these barriers to reporting may be changing due to changes in general practice. For example, QOF templates, requiring GP action to complete, were taking up time in the consultation that might previously have been used to make an ADR report.

Chapter 5 showed that PCTs with higher average QOF points appeared to be correlated to increased ADR reporting rates, showing that QOF may be a marker for good performance in ADR reporting. Interestingly, hospital medicines management criteria showed no similar relationship to ADR reporting rates. QOF also gives a potential model for bringing in a financial incentive for ADR reporting in general practice.

However, reporting GPs in the qualitative section of this thesis did not value payments for their ADR reports, seeing ADR reporting as a duty to the wider public or medical profession, or in response to guilt about the harm prescribed medicines cause. This thesis has attempted to draw a parallel between the Yellow Card scheme and the National Blood Transfusion Service, as described by Titmus's theory of "*gift relationships*". Such a relationship may be damaged by the introduction of a financial incentive.

Reporting GPs also seemed to be therapeutically conservative prescribers, sceptical of the pharmaceutical industry. Support for this qualitative finding also came from the analysis of the correlation between PCT prescribing rates and ADR reporting rates. The higher the prescribing rate within a PCT, the lower the ADR reporting rate. However, a more rigorous study examining individual GP prescribing and ADR reporting activity would give a more conclusive answer than the aggregated data used in this analysis.

The qualitative branch of research showed that feedback and reminders about the Yellow Card scheme were important for reporting GPs, re-enforcing their ADR reporting habit. Education was also important, although not always successful at creating a reporting GP. The study of undergraduate reporting in chapter 4 attempted to measure the presence of the Yellow Card scheme in undergraduate education of pharmacists and doctors. Results showed that the scheme was included in both medical and pharmacy curricula, but room existed for further involvement of the MHRA and regional YCCs in undergraduate education.

Early medical training takes place in the hospital environment. Chapter 5 examined hospital reporting within the West Midlands region and found wide variation in ADR reporting performance of hospitals. The survey of chief pharmacists in Chapter 3 found that ADR reporting was given a low priority by Drug and Therapeutic Committees, leading to a lack of institutional interest in ADR reporting. However, many hospital pharmacy schemes were in operation, and chief pharmacists were supportive of hospital pharmacy reporting. However,

there was concern about hospital pharmacists' training and time pressures leading to under-reporting.

The analysis of ADR reporting in the West Midlands in Chapter 5 showed hospital pharmacist reporting was continuing to rise, with no adverse effect on hospital doctor reporting. However, the study also showed that primary care ADR reporting was falling rapidly in the case of GPs, and community pharmacy reporting was still at a disappointingly low level. The West Midlands region had an increased reporting rate in comparison to national figures, which could be put down to the promotional and educational activities of the West Midlands YCC.

Nationally, healthcare professional ADR reporting appears to be in decline, falling to levels of reporting similar to that seen at the time of the withdrawal of benoxaprofen in the 1980s. One source of reports from primary care is the patient, and national reporting rates show a large influx of patient reports in 2006.

7.2. Recommendations for policy

A number of recommendations can be made based on the results of the present study:

- A period of stability is required for the Yellow Card scheme. Over the years a number of changes have been made to the structure of the MHRA, including the loss of established brand names. While knowledge of regulatory bodies may also be limited within healthcare professionals, the CSM had a high recognition and trust factor, as did *Current Problems in Pharmacovigilance*. The new CHM and the MHRA's new publication *Drug Safety Update* should not be changed for the foreseeable future, in order that similar recognition and trust is rebuilt over future years. Given the preference for paper given by GPs, consideration should be given to supplying *Drug*

Safety Update in a hard copy form to GPs, whose activity in the Yellow Card scheme has fallen rapidly in recent years.

- Introduction of a fee or financial target for Yellow Card reporting may be counter-productive, despite the temptation to copy the apparent success of QOF targets. Such a step would also be difficult to reverse, and also may have an adverse influence on other reporting groups, such as those based within secondary care.
- The MHRA should view all communications as marketing opportunities for the Yellow Card scheme. This includes acknowledgement letters, follow-up letters, additional information (such as DAPs) and email cascades alerts. The GP study found that cascade drug alert emails were not to the point, and often required the clicking of an additional link. A short précis of the alert should be included at the top of the email, with links provided for further information.
- In order to improve the effectiveness of acknowledgement letter to reporters, the MHRA should consider returning the task of sending of acknowledgement letters to the regional YCCs.
- While DAPs should continue to be available on the MHRA website, the present study found they were not valued highly by reporters, due to their size and complexity. Consideration should be given to shorter 2-page sheets that could summarise ADRs ranked in order of importance for professionals. However, these may create considerable additional work for the MHRA.

7.3. Ideas for future research

Considerable scope exists for further research into health professionals' interaction with the Yellow Card scheme. The present study has identified some areas that could warrant further study:

- Further examination of GP characteristics that are associated with ADR reporting.
The present study used PCT level data to investigate associations. Studies at the individual GP level between prescribing and ADR reporting rates could confirm if the high prescribers are low reporters to the scheme, and could consider patient factors that may also influence reporting.
- The study has highlighted training and reminders of the Yellow Card scheme as important to aid reporting. Controlled trials of educational interventions with proven effectiveness, such as academic detailing^{229,383-387}, could be carried out with various professional groups. Multi-centre studies involving the regional YCCs would be preferable.
- This study has highlighted a failure of current measures of medicines management with the hospital sector to encourage ADR reporting. Examination of techniques to improve institutional feedback to hospitals and PCTs should be considered.
- Prescribing advisors were noted as trusted individuals by GPs. Consideration should be given to testing their willingness and suitability to pass on reminders about the Yellow Card scheme, and examining any effect on GP reporting rates within PCT.
- Undergraduate education in pharmacy and medicine has expanded in the past 4 years, and in addition new healthcare professionals have been added to the Yellow Card scheme. A more detailed questionnaire concerning ADRs and Yellow Card reporting, could be sent out to schools of medicine, pharmacy and nursing to find the extent of the Yellow Card in course material.
- A quantitative postal survey based on the themes developed in the qualitative part of this thesis would be also of interest.

7.4. Conclusion

The present study has considerably has expanded the knowledge of the state of spontaneous reporting within the United Kingdom.

ADR reporting is widely covered in medical and pharmacy undergraduate education, with explicit mention of the Yellow Card scheme and its use in course assessments. However, it is not known to what extent other groups, such as nurses, are exposed to the Yellow Card scheme and key concepts in pharmacovigilance. As the extension of prescribing rights continues, it is increasingly important to make healthcare professionals aware of the importance of spontaneous reporting in their formative years.

Within acute NHS hospital trusts the present study has identified a low institutional interest in the wider public safety of patients from harms caused by medicines. ADR reporting is not a priority within NHS trusts, and nor do current medicines management criteria used by the Healthcare Commission focus on ADRs. Hospital pharmacist reporting has become established in the past ten years, and has not reduced reports from hospital doctors. The findings of the survey of chief pharmacists do expose concerns about training of pharmacists to detect ADRs, perhaps also reflected in hospital pharmacists' focus on serious reactions to established drugs. Hospital pharmacist reporting in the West Midlands region is driven by a small number of committed reporters. Although it is not know how representative this is of the national reporting figures for hospital pharmacists, it could indicate that ADR reporting is yet to become a more widespread activity seen as part of everyday activity. Nurse reporting is producing a smaller number of reports in the hospital sector, but such reports do seem focused on black triangle drugs (possibly related to nursing specialists).

In primary care, the present study has confirmed the rapid decline in reporting by GPs over the past ten years. The introduction of community pharmacist reporting in 1999 has not made

up this shortfall to any significant extent. The fall in reporting from GPs is the primary reason for continuing falls in the number of reports from healthcare professionals, creating changes in the nature of the data reported to the MHRA. In past two years, large drops in healthcare professional reporting have occurred, but these have been masked by a large influx of patient reports to the Yellow Card scheme. Patient reporting is a priority for the MHRA, and it is likely that it will increase in importance, especially if falls in healthcare professional reporting cannot be halted.

The present study also examined in depth the attitudes of GPs to the Yellow Card scheme, developing a grounded theory for the interaction of GPs with the Yellow Card scheme. Falls in GP reporting may be due to changes in the general practice environment, first triggered by the formation of the internal market in 1991, and later by the use of more target-driven contract structures. Such changes may have crowded out altruistic public service notions that drive Yellow Card reporting. The 2004 GP contract also may have changed the nature of the consultation, and reduced opportunities for completion of a Yellow Card.

A key finding of the qualitative arm of this study has been the nature of the duty felt towards the Yellow Card scheme, which drives GP reporting. Nurturing this altruistic motivation may improve interest in the Yellow Card scheme. Introduction of financial fixes to increase reporting may not necessarily improve reporting rates and could be counterproductive, further undermining altruistic motivations.

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Appendix I

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Appendix II

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Appendix III: Chief Pharmacist's questionnaire

Adverse Drug Reactions: Questionnaire of UK Chief Pharmacists

West Midlands Centre for Adverse Drug Reaction
Reporting (CADRE) and Aston University's
Pharmacy Practice Group.



If you have been unable to fill in this questionnaire please state the reason here and post the survey to the address below in the envelope enclosed.

I have not filled in this questionnaire because:

- ☐ of a lack of time.
- ☐ the subject is unimportant.
- ☐ it is sensitive information.
- ☐ I never complete questionnaires.
- ☐ of other reasons.

State other reason(s) _____

If you have any questions about this questionnaire please contact:

Anthony Cox,
Pharmacy Practice Group,
School of Pharmacy,
Aston University,
Birmingham,
B4 7ET

Email: anthony.cox@cityhospbham.wmids.nhs.uk
Phone: 0121 507 5672

Definitions:

The phrase "**your trust**" refers to the trust at which you have managerial responsibility for pharmacy services.

About Your Trust

Question 1. Is your trust affiliated to a Medical School?

Yes ☐ No ☐ Don't know ☐

Question 2. Does your trust have a medicines management control device (e.g. Drug and Therapeutics committee) ?

Yes ☐ No ☐ Don't know ☐

My trust has more than one medicines management control device ☐

Question 3. If you answered yes to **Question 2**, has Adverse Drug Reaction (ADR) reporting been on the agenda of the medicines management control device(s) in the past two years?

Yes ☐ No ☐ Don't know ☐

Question 4. In your opinion what priority on does the medicines management control device(s) give to ADR reporting on a scale of 0 to 5? (0=very low 5 =very high)

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

Question 5. Is there a member of medical staff who takes a lead in ADR reporting within your trust?

Yes ☐ No ☐ Don't know ☐

Question 6. If you answered yes to **Question 5**, How does this manifest itself?

Medical meetings ☐ Bulletins ☐

Other ☐ Please state: _____

Benchmarking schemes

Question 7

a. Are you a member of a national benchmarking scheme? Yes ☐ No ☐

b. If so, does this scheme ask for ADR reporting rates? Yes ☐ No ☐

Question 8

a. Are you a member of a local benchmarking scheme? Yes ☐ No ☐

b. If so, does this scheme ask for ADR reporting rates? Yes ☐ No ☐

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Local ADR Reporting Schemes

Question 1. Does your trust have a local scheme for adverse drug reaction (ADR) reporting?

Yes ☐ No ☐ Don't know ☐

Question 2. Which of the following groups is encouraged to report to the scheme

Medical staff ☐ Nursing staff ☐ Pharmacists ☐

Professions allied to medicine (PAMs) ☐ Patients ☐

Other ☐ Please state _____

Question 3. If a local scheme exists, can individual reporters deviate from this policy?

Yes ☐ No ☐ Don't know ☐

Question 4. If you have no local ADR reporting scheme, in your opinion how likely is the development of a local scheme in the future?

Definite ☐ Possible ☐ Unlikely ☐ Will not happen ☐

Question 5. Have you been made aware of specific cases where pharmacist ADR reporting has been the cause of a complaint from medical staff?

Yes ☐ No ☐

If "Yes" please state the nature of the concerns

Question 6. Have you been made aware of specific cases where pharmacist ADR reporting has been the cause of a complaint from a patient?

Yes ☐ No ☐

If "Yes" please state the nature of the complaint

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Your views on ADR reporting

Please indicate your agreement with the following statements by ticking the appropriate box

a. ADR reporting is an essential component of a pharmacists role on the wards

Strongly agree ☐ Agree ☐ Not sure ☐ Disagree ☐ Strongly Disagree ☐

b. Pharmacist ADR reports should be reviewed by the pharmacy department before being sent to the CSM

Strongly agree ☐ Agree ☐ Not sure ☐ Disagree ☐ Strongly Disagree ☐

c. Monitoring of adverse drug reactions within my trust is a clinical governance issue.

Strongly agree ☐ Agree ☐ Not sure ☐ Disagree ☐ Strongly Disagree ☐

d. Monitoring of adverse drug reactions should be a priority for pharmacy services.

Strongly agree ☐ Agree ☐ Not sure ☐ Disagree ☐ Strongly Disagree ☐

e. Pharmacists would benefit from increased training on ADR reporting.

Strongly agree ☐ Agree ☐ Not sure ☐ Disagree ☐ Strongly Disagree ☐

f. Pharmacists within my trust have the competency to detect ADRs

Strongly agree ☐ Agree ☐ Not sure ☐ Disagree ☐ Strongly Disagree ☐

g. Increased pharmacist time on wards in a clinical capacity would increase ADR reporting by pharmacists.

Strongly agree ☐ Agree ☐ Not sure ☐ Disagree ☐ Strongly Disagree ☐

h. Development of a local ADR reporting scheme is not a valid use of staff resources.

Strongly agree ☐ Agree ☐ Not sure ☐ Disagree ☐ Strongly Disagree ☐

i. ADR reporting is a priority of my line manager

Strongly agree ☐ Agree ☐ Not sure ☐ Disagree ☐ Strongly Disagree ☐

j. ADR reporting is a one of my priorities.

Strongly agree ☐ Agree ☐ Not sure ☐ Disagree ☐ Strongly Disagree ☐

k. ADR reporting is a priority of my clinical services pharmacist(s).

Strongly agree ☐ Agree ☐ Not sure ☐ Disagree ☐ Strongly Disagree ☐

l. ADR reporting is not seen as a priority by pharmacists in my trust.

Strongly agree ☐ Agree ☐ Not sure ☐ Disagree ☐ Strongly Disagree ☐

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m. It is a professional responsibility of pharmacists to report ADRs.

Strongly agree ☐ Agree ☐ Not sure ☐ Disagree ☐ Strongly Disagree ☐

n. Pharmacists have the active support of medical staff to report ADRs.

Strongly agree ☐ Agree ☐ Not sure ☐ Disagree ☐ Strongly Disagree ☐

o. Pharmacists have the active support of the pharmacy department to report ADRs.

Strongly agree ☐ Agree ☐ Not sure ☐ Disagree ☐ Strongly Disagree ☐

p. Current recruitment and retention difficulties are inhibiting pharmacist ADR reporting

Strongly agree ☐ Agree ☐ Not sure ☐ Disagree ☐ Strongly Disagree ☐

Name _____

Gender: Male ☐ Female ☐

Number of years registered: _____ Number of years in present post: _____

Thank you, your time and effort is much appreciated. Please return the completed questionnaire using the pre-paid envelope provided.

If you have any further comments, please feel free to write them below:

[illegible]

Number

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Survey of Adverse Drug Reaction Teaching of UK Pharmacy Undergraduates

West Midlands Centre for Adverse Drug Reaction
Reporting (CADRE) and Aston University's
Pharmacy Practice Group.



To avoid being sent a reminder we would like to know why you have been unable to fill in this survey. Please state the reason here and post the survey to the address below in the Freepost envelope enclosed.

I have not filled in this survey because:

- ☐ of a lack of time.
- ☐ the subject is unimportant.
- ☐ it is sensitive information.
- ☐ I never complete surveys.
- ☐ of other reasons.

State other reason(s) _____

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**Survey of Adverse Drug Reaction Teaching of UK
Pharmacy Undergraduates**

QUESTION 1:

How many individuals are responsible for teaching pharmacy students about adverse drug reactions within your School?

None ☐ One ☐ Two ☐ Three or more ☐ Don't know ☐

If 'None' or 'Don't know' go to question 3

QUESTION 2:

What is(are) the subject specialisations(s) of the individual(s) responsible for this teaching? (e.g. toxicology, pharmacology, practice)

QUESTION 3:

Does your undergraduate pharmacy syllabus mention the Yellow Card Scheme for adverse drug reaction reporting?

Yes ☐ No ☐ Don't know ☐

If so, in which year of the course is it mentioned?

Year _____

QUESTION 4:

Do you have specialist speakers, from outside of the university staff, who teach on practical aspects of the Yellow Card Scheme?

Yes ☐ No ☐ Don't know ☐

QUESTION 5:

If you stated Yes to Question 4, please state the organisation in which they work principally

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QUESTION 6:

Do your course assessments ever contain questions about the Yellow Card Scheme?

Yes ☐ No ☐ Don't know ☐

QUESTION 7:

In your view would it be helpful if students received as part of their training:

A guide to reporting to the Yellow Card Scheme

Yes ☐ No ☐ Don't know ☐ Already receiving ☐

A Yellow Card

Yes ☐ No ☐ Don't know ☐ Already receiving ☐

Copies of *Current Problems in Pharmacovigilance*

Yes ☐ No ☐ Don't know ☐ Already receiving ☐

Any other comments:

Thank you for your time, please place the completed survey in the envelope provided and return to the address below.

Number

Anthony Cox, Pharmacy Practice Group,
School of Pharmacy, Aston University, Birmingham B4 7ET



Aston University

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protection purposes

Appendix VII

List of Primary ICD 10 codes related to medication use.

D59.0 Drug-induced autoimmune haemolytic anemia
D59.2 Drug-induced nonautoimmune haemolytic anaemia
D61.1 Drug-induced aplastic anaemia
E03.2 Hypothyroidism due medicaments and other exogenous substances
E24.2 Drug-induced Cushing's syndrome
E27.3 Drug-induced adrenocortical insufficiency
F11.0 Mental and behavioural disorders due to use of opioids - acute intoxication
F11.1 Mental and behavioural disorders due to use of opioids - harmful use
F11.2 Mental and behavioural disorders due to use of opioids - dependence syndrome
F11.3 Mental and behavioural disorders due to use of opioids - withdrawal state
F11.4 Mental and behavioural disorders due to use of opioids -withdrawal state with delirium
F11.5 Mental and behavioural disorders due to use of opioids - psychotic disorder
F11.6 Mental and behavioural disorders due to use of opioids - amnesic syndrome
F11.7 Mental and behavioural disorders due to use of opioids - residual and late onset psychotic disorder
F11.8 Mental and behavioural disorders due to use of opioids - other mental and behavioural disorders
F11.9 Mental and behavioural disorders due to use of opioids - unspecified mental and behavioural disorder
F13.0 Mental and behavioural disorders due use sedatives/hypnotics - acute intoxication
F13.1 Mental and behavioural disorders due use sedatives/hypnotics- harmful use
F13.2 Mental and behavioural disorders due use sedatives/hypnotics- dependence syndrome
F13.3 Mental and behavioural disorders due use sedatives/hypnotics- withdrawal state
F13.4 Mental and behavioural disorders due use sedatives/hypnotics -withdrawal state with delirium
F13.5 Mental and behavioural disorders due use sedatives/hypnotics - psychotic disorder
F13.6 Mental and behavioural disorders due use sedatives/hypnotics - amnesic syndrome
F13.7 Mental and behavioural disorders due use sedatives/hypnotics - residual and late onset psychotic disorder
F13.8 Mental and behavioural disorders due use sedatives/hypnotics- other mental and behavioural disorders
F13.9 Mental and behavioural disorders due use sedatives/hypnotics - unspecified mental and behavioural disorder
F19.0 Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances - acute intoxication
F19.1 Mental and behavioural disorders due to multiple drug use and use of other psychotic substances- harmful use
F19.2 Mental and behavioural disorders due to multiple drug use and use of other psychotic substances- dependence syndrome
F19.3 Mental and behavioural disorders due to multiple drug use and use of other psychotic substances- withdrawal state
F19.4 Mental and behavioural disorders due to multiple drug use and use of other psychotic substances - withdrawal state with delirium
F19.5 Mental and behavioural disorders due to multiple drug use and use of other psychotic substances - psychotic disorder

F19.6 Mental and behavioural disorders due to multiple drug use and use of other psychotic substances - amnesic syndrome
F19.7 Mental and behavioural disorders due to multiple drug use and use of other psychotic substances - residual and late onset psychotic disorder
F19.8 Mental and behavioural disorders due to multiple drug use and use of other psychotic substances- other mental and behavioural disorders
F19.9 Mental and behavioural disorders due to multiple drug use and use of other psychotic substances - unspecified mental and behavioural disorder
G21.1 drug-induced secondary parkinsonism
G24.0 Drug-induced dystonia
G25.1 Drug-induced tremour
G25.4 Drug-induced chorea
G25.6 Drug-induced tics and other tics of organic origin
G72.0 Drug-induced myopathy
H91.0 Ototoxic hearing loss
I42.7 Cardiomyopathy due to drugs and other external agents
J70.2 Acute drug-induced interstitial lung disorders
J70.3 Chronic drug-induced interstitial lung disorders
J70.4 Drug-induced interstitial lung disorders, unspecified
K71.0 Toxic liver disease with cholestasis
K71.1 Toxic liver disease with hepatic necrosis
K71.2 Toxic liver disease with acute hepatitis
K71.3 Toxic liver disease with chronic persistent hepatitis
K71.5 Toxic liver disease with chronic active hepatitis
K71.6 Toxic liver disease with hepatitis, not elsewhere classified
K71.7 Toxic liver disease with fibrosis and cirrhosis of liver
K71.8 Toxic liver disease with other disorders of liver
K71.9 Toxic liver disease - unspecified
L56.1 Drug photoallergic response
M10.2 Drug-induced gout
M32.0 Drug-induced Systemic lupus erythematosus
M34.2 Systemic sclerosis induced by drugs
N14.0 analgesic nephropathy
N14.1 nephropathy induced by other drug, medicament or biological substances
N14.2 nephropathy induced by unspecified drug, medicament or biological substances
T88.3 Malignant hyperthermia due to anaesthesia
T88.6 anaphylactic shock due to adverse effect of correct drug or medicament properly administered
T88.7 Unspecified adverse effect of drug or medicament

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Appendix X

Memo example

1:00 pm, Jul 17, 2007. Serious in non-reporters

When pressed about the types of things that should be reported, non-reporters rated seriousness highly. However, if well known then seriousness becomes less important.

Note that serious reactions are dealt with at the hospital, so GPs have no need to report.

Haemorrhage wouldn't be reported as it is a failure of monitoring or a drug interaction issue.

Aware that black triangle reports do not need to be serious.

THOUGHT: two types of concerns about seriousness. Is it serious enough

The MHRA would be interested and is it serious enough that they will be interested?

Appendix XI

Topic guide

Opening Questions – for all GPs

What is your understanding of the Yellow Card Scheme for adverse drug reactions?

Have you seen any adverse drug reactions recently?

What is your view of usefulness of the Yellow Card scheme?

Do you find the reporting criteria clear?

Is there anything you would definitely report?

What do you think the value of reports are?

You're quite a high reporter to the scheme, can you point to any motivating factors that make you want to report? Or things in the past that may have made you interested?

Would a fee per Yellow Card increase your participation in the Yellow Card Scheme?

Legal requirement?

Do you have any advice on how the Yellow Card Scheme could be improved?

Are you aware of the on-line reporting scheme yellowcard.gov.uk

Are there things about your work, or environment, which help reporting?

Are there things about your work, or environment, which hinder reporting?

What competing pressures do you see in primary care? Follow-up QOF.

Do you have any concerns about reporting adverse drug reactions?

Had you heard of the West Midlands CSM, prior to our letter? Follow-up : All cards to London.

What's your opinion of the regional monitoring centres?

Opinion: MHRA?

Feedback Current problems in pharmacovigilance etc DAPS.

Do patients volunteer reports? Do you always accept them?

Patient reporting is currently being piloted, do you have any views on it?

Drug safety issues raised by the MHRA, are they clearly communicated to you?

ADRs are in the media a lot, either to drugs or vaccines, do you find that an issue in practice?

Recognition or willingness, which is more important?

How do you think the government and MHRA handle these issues?

Herbal reactions?

Encouraging colleagues?

What about other reporting schemes, how do you think they will impact?

Demographics: Age, years as GP, educational role.

Closing questions – for all GPs

Are there any other issues that you think are important and which you think I should have asked you about?

Do you have any questions you want to ask me?

Appendix XII

Consent form for GP study

Participant Identification Number for this study:

Consent form

Title of Project: Why doctors report adverse reactions: A Qualitative Study

Name of Researcher: Anthony R Cox

Please initial each box

1. I confirm that I have read and understood the information sheet dated..... (Version.....2.....) for the above study and have had the opportunity to ask questions.

☐

2. I understand my participation is voluntary and that I am free to withdraw at any time, without giving any reason.

☐

3. I agree to the recording of the interview.

☐

4. I agree to take part in the above study.

☐

Dr xxxxxxxxxxxx

Name of participant

Date

Signature

Anthony Cox

Researcher

Date

Signature

Version 2 – November 2005

Anthony Cox

Appendix XIII

Tests for parametric data

PCT Variable	Z_{skewness}	Z_{kurtosis}	Kolmogorov-Smirnov test	Parametric or non-parametric data
Average QOF Clinical Domain	-1.97	-0.14	D 0.142(30) P=0.123	Parametric
Average Organisational Domain	-0.83	-1.39	D 0.133(30) P=0.188	Parametric
Average QOF Medicines Management Domain	-0.44	-1.05	D 0.103(30) P=0.2	Parametric
Average Total QOF points	-0.73	-1.34	D 0.155(30) P=0.063	Parametric
Top Ten reported drugs – total prescriptions	1.33	-1.21	D 0.203(30) P=0.003	Non-parametric
All drugs – total prescriptions	1.43	0.93	D 0.162(30) P=0.043	Non-parametric
Top Ten reported drugs – total prescriptions SQR RT transform	0.75	-1.32	D 0.163(30) P=0.04	Non-parametric
All drugs – total prescriptions SQR RT transform	0.87	-1.26	D 0.132(30) P=0.194	Parametric
All drugs – Total Yellow Card reports	2.99	2.97	D 0.144(30) P=0.122	Non-parametric
All drugs – All reports SQR RT transform	0.48	0.38	D 0.096(30) P=0.2	Parametric
Top Ten drugs – Total Yellow Card reports	4.24	6.36	D 0.151(30) P=0.079	Non-Parametric
Top Ten drugs – All reports SQR RT transform	-0.22	1.25	D 0.125(30) P=0.2	Parametric
Top Ten Drugs – Prescriptions per 1000 population	0.67	0.67	D 0.124(30) P=0.2	Parametric
All drugs – Prescriptions per 1000 population	1.87	1.02	D 0.131(30) P=0.198	Parametric
Top Ten Drugs – Yellow Card reports per 1000 prescriptions	5.18	9.27	D 0.185(30) P=0.01	Non-Parametric
All Drugs – Yellow Card reports per 1000 prescriptions	3.14	4.22	D 0.166(30) P=0.035	Non-parametric
Top Ten Drugs – Yellow Card reports per 1000	-0.14	2.24	D 0.149(30) P=0.087	Parametric

prescriptions SQR RT transformation				
All Drugs – Yellow Card reports per 1000 prescriptions SQR RT transformation	0.29	1.59	D 0.134(30) P=0.178	Parametric
Top Ten Drugs – Yellow Card reports per 1,000,000 population	3.98	5.71	D 0.185(30) P=0.01	Non-parametric
All Drugs – Yellow Card reports per 1,000,000 population	3.35	4.63	D 0.212(30) P=0.001	Non-parametric
Top Ten Drugs – Yellow Card reports per 1,000,000 population SQR RT + 2 transformation	1.00 7	1.85	D 0.153(30) P=0.07	Parametric
All Drugs – Yellow Card reports per 1,000,000 population SQR RT transformation	0.61	2.3	D 0.174(30) P=0.021	Non-Parametric
Population	1.73	-0.22	D 0.148(30) P=0.092	Parametric
Average List Size	-0.45	-0.59	D 0.121(30) P=0.2	Parametric
Percentage Single Handed	0.34	-1.38	D 0.129(30) P=0.2	Parametric
Percentage Male	-1.12	-0.65	D 0.107(30) P=0.2	Parametric
Percentage of General Practitioners over 55 years of age	1.68	-0.25	D 0.172(30) P=0.024	Non-parametric
Percentage of population over 65	-3.05	4.52	D 0.14(30) P=0.16	Non-parametric
Deprivation index 2004	2.09	0.31	D 0.19(30) P<0.05	Non-parametric
Health deprivation score	0.37	-1.04	D 0.10(30) P=0.02	Parametric
Percentage of General Practitioners over 55 years of age SQR RT	0.79	-0.98	D 0.149(30) P=0.088	Parametric