

*Independent Scientific
Advisory Committee for
Medicines and Healthcare
products Regulatory Agency
(MHRA) database research*

(ISAC)

2nd Annual Report

April 2007-March 2008

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Foreword from the Chairman of the MHRA

It gives me great pleasure to present the ISAC Annual Report for 2006-2007. This has been another year in which the Committee has provided high quality advice on a broad range of issues. It is hard to believe that the Committee has only been in existence for two years now that it has quickly become an established part of the research community and MHRA business.

I am pleased that another round of recruitment attracted a large amount of interest and led to the appointment of further members with expertise in paediatrics, pharmacovigilance, epidemiology and a new chairman. The Committee is now equipped to offer advice on a broad range of subject areas.

I would like to take this opportunity to put on record my gratitude to Dr Brian Gennery for chairing the Committee for its first two years. His experience as the past Chairman of the Scientific and Ethical Advisory Group was invaluable in ensuring that there was a smooth transition to a formal review process that encompassed GPRD and Yellow Card data. We wish him the best for his retirement and welcome on board Prof Jennifer Adgey who joins us at a time when the use of government data is under more scrutiny than ever.

I would like to thank the Chairmen and Members for their hard and invaluable work, ensuring that researchers around the world have access to MHRA data and ensuring that the databases we hold on behalf of the public are used for their benefit.

Professor Sir Alasdair Breckenridge
MHRA Chairman
June 2008

Foreword from the Chairman of the ISAC

I was delighted to be appointed Chairman of the ISAC earlier this year.

A lot of hard work has clearly gone into establishing the processes of review for the Committee and it has an excellent record of providing high quality and timely review. I am proud to serve on a Committee that has quickly earned such a good reputation.

I have soon learnt that applications can be about virtually any medicine or medical condition and am pleased to have such a broad base of expertise among Committee members on which to draw. The input of lay members is particularly welcome as they raise issues from a patient perspective that would otherwise be missed. In a patient-centred NHS it is vital we keep the interests of patients and the public at the centre of decision making.

I am pleased that the MRC initiative has been such a success and that it has opened up the GPRD database more widely. I am keen to ensure that all the research community is made more aware of the MHRA data available to them so that the number of Yellow Card and GPRD applications will continue to increase.

I am grateful to my predecessor as well as other members and the Secretariat for the induction they have given me on handling protocol review. I look forward to working with them closely during my term of office and ensuring MHRA data is widely used to benefit public health.

Professor Jennifer Adgey
June 2008

1. **Introducing the Independent Scientific Advisory Committee for MHRA database research**

1.1. **ISAC's role and Terms of Reference**

The ISAC was established by the Secretary of State for Health in February 2006 to review the scientific merit of proposals for research using data from the MHRA General Practice Research Database (GPRD) and Yellow Card Scheme database.

The functions of the ISAC are:

- to consider and provide advice to MHRA on applications for Yellow Card data which fall outside Freedom of Information provisions, and all research projects which propose the use of data from the General Practice Research Database;
- to provide advice at the request of the MHRA on wider aspects of the release of Yellow Card data;
- to provide advice at the request of the MHRA on new specific uses of data from the General Practice Research Database.

1.2. **Membership and operation of the ISAC**

At the end of the reporting period there were thirteen professional ISAC members, chaired by Professor Jennifer Adgey, with expertise in statistics, epidemiology, general practice, paediatrics and clinical pharmacology. There are also two lay members. The Committee was chaired until 31 December 2007 by Dr Brian Gennery. Until the appointment of Dr Ruben Thanacoody from YCC Scotland in January 2008, a Yellow Card Centre Head was invited as an expert in the Yellow Card Scheme when a Yellow Card application was being considered. Full information on membership is included at Annex 1.

Following a successful pilot in 2007, the Committee reviews GPRD protocols using a two-team system. Protocols are circulated alternately to each team and members review and submit feedback individually to the Chairman. Protocols that require revision and resubmission are circulated to the Chairman only for a final decision. Yellow Card applications are considered only at ISAC meetings.

1.3. **Review of Yellow Card Applications**

Using the principles of the Data Protection Act 1998 (DPA) and Freedom of Information Act 2000 (FOIA), requests for Yellow Card data have been divided into Category I requests that are generally releasable under the FOIA and not prohibited from release by DPA, and Category II requests that are subject to FOIA exemptions and the restrictions of the DPA.

The ISAC reviews the scientific aspects of requests for Category II data. The Committee does not have access to the data being requested, but considers whether or not the MHRA should collate and supply these data, bearing in mind the founding principles of the Yellow Card Scheme (Annex 3).

When reviewing Yellow Card applications the Committee considers whether:

- the methodology of the study is sound;
- Yellow Card data can address the hypothesis;
- the study is of potential scientific value and/or has significant public health implications;
- the use of other data sources could, together with Yellow Card data, identify patients or reporters;
- ethical review from a NHS REC is required; and
- there are any FOI/DPA reasons why data should not be released.

1.4. Review of GPRD protocols

When reviewing GPRD protocols the Committee considers whether:

- There is compliance with the requirement to ensure protection of practice and patient confidentiality;
- There is a well defined hypothesis or clear question to be addressed;
- The GPRD is a suitable database in which to conduct the research;
- The methodology is considered appropriate, including consideration of possible bias and confounding; and
- Original case record verification is necessary.

2. Achievements of the second year

2.1. Outputs

- The Committee met four times and reviewed a total of 114 GPRD protocols (electronically) and 3 Yellow Card applications for the first time. (see *Chapter.5*)
- Of the total number of GPRD protocols reviewed, 36 sought data accessed under the GPRD -Medical Research Council (MRC) scheme.
- Advised MHRA on wording of letters requesting that Yellow card reporters and patients participate in research projects.
- Advised the MHRA on a response to the Ministry of Justice independent review of the use and sharing of personal information in the public and private sectors. This review would consider whether there should be any changes to the Data Protection Act 1998 and the options for implementing any such changes.
- Revision of the procedures for continuing review of GPRD research protocols previously approved under SEAG (Scientific and Ethical Advisory Group).
- Withdrawal of approval for all GPRD studies that may be undertaken on the basis of blanket approval previously granted under SEAG; rationalisation of the process for dealing with such applications.

2.2. Highlights of the second year's meetings

The four meetings held in the period covered by the second annual report were on Thursday 10 May 2007, Friday 6 July 2007, Friday 26 October 2007 and Thursday 31 January 2008. Summary minutes of all these meetings have been published on the MHRA website.¹ The first part of the meeting on 31 January 2008 was an induction for the additional members recruited that month. Meetings are structured with general discussion items followed by separate sections for Yellow Card and GPRD applications. Key issues discussed in meetings during the second year are outlined below.

2.2.1. Strengthening the Yellow Card Scheme

The Committee was informed of work the Agency was doing to increase Yellow Card reporting rates and raise awareness of the Scheme with advice from the Yellow Card Working Group of the Pharmacovigilance expert advisory group of the Commission on Human Medicines. The Committee offered advice on the strategy and stressed the importance of involving patients and the public by targeting them through non-health related broadcast and print media. Increased awareness of the Scheme might also make the research community more aware that Yellow Card data can be used for research.

¹ http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=930

2.2.2. Data Mining in GPRD

Prof David Hand, Professor of Statistics and Head of the Statistics Section in the Department of Mathematics, Imperial College London and President of the Royal Statistical Society (RSS) 2007 – 2009 gave a presentation on data mining methodology and introduced discussion on this topic. This was in response to concerns that the ISAC may be required to consider applications to access the GPRD for data mining purposes in the future.

2.2.3. Research Governance and the GPRD

To align its functions more closely with the UK National Health Service (NHS) governance framework for undertaking research, and the Multiple Research Ethics Committee (MREC) approval that underpins the operations of the GPRD, the ISAC adopted a number of operational changes relating to the protocol review and approval process. Changes in policy related to requests for amendment to protocols and blanket approval of protocols.

In the past year, the Committee noted that on a number of occasions, applications were made for amendments or additions to approved protocols. The Committee was concerned that some of these amendments were not within the scope or closely enough related to the original protocol. The Committee will watch this closely as significant deviations from the approved protocol undermine the safeguards the Committee was designed to deliver. Amendments will only be considered if they are to modify the methods to be used to answer the approved research question

2.2.4. External Data Linkage in GPRD

In response to the GPRD initiative to link primary care data to other external data sources, the ISAC have raised and discussed issues of patient confidentiality and data security with the Director of GPRD. MREC approval for the linkage has already been secured by the GPRD and the data linkage process is being undertaken by a trusted third party. The ISAC application form was updated to take into account requests for access to GPRD linked data.

2.2.5. Use of GPRD data for training purposes

The Committee discussed and supported the use of GPRD data by external bodies to undertake training. The exception was the use of data accessed under the GPRD-MRC initiative which prohibits the data to be used for teaching or training purposes.

2.2.6. Age discrimination and the use of GPRD data

The Committee was particularly concerned that researchers using GPRD data might be inadvertently excluding important groups of patients from their research because of proposed age selection criterion. Researchers were actively encouraged through reviewer's feedback to provide the rationale for age-related inclusions or exclusions in their study.

3. How the ISAC is organised

3.1. Secretariat

There are two ISAC secretaries, one for GPRD issues and one for Yellow Card issues. This is to ensure there is a “Chinese Wall” between the review of GPRD protocols and the regulatory staff of Vigilance and Risk Management of Medicines Division (VRMM) division who provide secretariat for Yellow Card applications.

GPRD queries can be sent to isac@gprd.com

Yellow Card queries can be sent to isacyellowcarddata@mhra.gsi.gov.uk

Further information on the Committee and Secretariat is on the MHRA website at:

http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=928

3.2. Meetings

ISAC meetings are usually held four times per year at the MHRA offices at Market Towers, 1 Nine Elms Lane, London SW8 5NQ. Meetings are not held in public to protect the confidentiality of applicants. Members access papers through the MHRA portal which is more secure than using email, or hard copy by Royal Mail Special Delivery.

3.3. Electronic working between meetings

Due to the tight deadlines for review and the volume received, review of the majority of GPRD protocols is performed electronically between meetings, with responses coordinated by the Chairman. Yellow Card applications are only reviewed at meetings.

3.4. Costs

Members are entitled to claim a fee for every meeting.

Fees payable until 31 December 2007 were:

	Committee Chair	Committee Members
Preparation	£81	£66
Attendance	£129	£108

Fees payable from 1 January 2008 are:

	Committee Chair	Committee Members
Preparation and attendance	£275	£174

In addition members are entitled to claim travel and subsistence expenses as follows:

- Travel expenses to and from home to the meeting venue;
- Travel and subsistence expenses incurred as part of the work of the ISAC away from the normal venue;
- Particular travelling costs associated to disabled members;
- Other reasonable expenses incurred e.g. locum costs, child care, overnight stay subject to agreed Agency limits.

3.5. Appointment of members

Members of the ISAC are appointed by the Appointments Commission (formerly NHS Appointments Commission). Members of the Committee hold office for a period of three years. The MHRA appoints a Chairman from the professional members. Full information on current membership is at Annex 1 and duties of members are at Annex 2.

3.6. Declaration of Interests

Members of the ISAC are required to follow the same code of practice on relationships with the pharmaceutical industry that has been developed for members of the Commission on Human Medicine and its Expert Advisory Groups. Members of the Committee are required to declare any relevant interests on appointment and to notify the MHRA of any changes immediately. Committee members have to declare their interests and those of their immediate family, and any other interests that may affect their impartiality or be perceived as doing so. Failure to comply with the Code of Practice will result in removal of an individual from the Committee.

Additionally, members are asked to declare any potential conflict of interest relevant to individual protocols at the time of protocol review. This allows interests to be taken into account during protocol review, therefore reducing potential bias in connection with these interests. ISAC members are excluded from participation in the review of protocols and applications arising from their own academic department. There is a Deputy Chairman for cases where the Chairman has a conflict of interest. A full declaration of members' interests is at Annex 5.

3.7. Appraisals

It is a condition of appointment that members engage in an annual appraisal process with the Chairman. The first appraisal period was February 2006-October 2007.

3.8. Freedom of Information and Publication scheme

Summary minutes of meetings are published on the MHRA website once full minutes have been agreed. Unless a FOI exemption applies, general sections of the minutes are published in full. Information on applications is only included in summary minutes when an application has been approved. If approved, the title/subject of the study and ISAC's conclusion would be published in summary minutes. The Committee considered that public health

scares could result if it became known that a researcher wanted data to look into certain issues, for example possible reactions to a vaccine. Publishing that a researcher wanted to look into reaction X of drug Y using Yellow Card or GPRD data could lead to media stories that certain medicines might be unsafe, before any research had been done and some years before any conclusions might be published. This could also lead to doubts in prescribers' minds about the safety of certain medicines. For this reason, names of drug(s) or reaction(s) to be studied are included in summary minutes, but never drug and reaction together.

If further information was requested from the applicant or the application was rejected, then no information on the study is published in summary minutes, other than the number of applications considered at that meeting. This is to protect the confidentiality/reputation of applicants and because applicants may wish to resubmit a new application.

The annual reports of ISAC will be made available on the MHRA website. Reporting periods are 1 April-31 March, but the first report was from 1 February 2006 to 31 March 2007 because of the date the Committee was established.

3.9. Appeal process

If applicants disagree with the outcome of an ISAC application, and this cannot be resolved by minor revision of the application or resubmission, then they can appeal. The appeal process is at Annex 6.

4. Applications considered by the ISAC from 1 April 2007-31 March 2008

4.1. Yellow Card

4.1.1. Total number of applications submitted to ISAC for the first time Apr 2007-Mar 2008

3

4.1.2. Number of applications submitted to ISAC for the first time Apr 2007-Mar 2008, by type of organisation to which the study's principal investigator was affiliated

Organisation Type	Number of submissions	Percentage of total
Academia	3	100%

4.1.3. Total number of applications approved by ISAC Apr 2007-Mar 2008

3

4.1.4. Total number of applications rejected by ISAC Apr 2007-Mar 2008

0

4.1.5. Total number of requests for further information requested by ISAC Apr 2007-Mar 2008

0

4.1.6. Information on applications approved by ISAC Apr 2007-Mar 2008

Ref	Applicant	Title	Affiliation
AYCD013	Professor Neil McIntosh	Active surveillance of adverse drug reactions in Scottish children: a proof of concept study	RCPCH
AYCD014	Prof Nick Bateman	Epidemiological Study of Adverse Drug Reactions in Scottish hospitals using ICD-10 discharge coding of hospital admissions	University of Edinburgh
AYCD015	Prof Tony Avery	Evaluation of patient Yellow Card reporting	University of Nottingham

Under the ISAC's remit to advise MHRA on "wider aspects of the release of Yellow Card data", the MHRA also shared an Information Paper with ISAC

on application AYCD16 *Psychotropic medication in paediatric populations* from the London School of Hygiene and Tropical Medicine.

4.1.7. Publications

A further publication using Type II Yellow Card research was published during the year. This was by Professor Ron Mann from application AYCD008. It was published under the title "An instructive example of a long-latency adverse drug reaction – sclerosing peritonitis due to practolol". The paper was published in *Pharmacoepidemiology & Drug Safety* 2007;**16**:1211-1216.

In January 2008 the MHRA Drug Safety Bulletin had a feature on the ISAC (Vol 1, Issue 6).

4.2. GPRD : Consideration of applications

4.2.1. During the period Apr 2007-Mar 2008, ISAC considered 114 new protocols and 3 questionnaires. Tables 1 and 2 show a breakdown of these protocols by study type and organisation to which the principal investigator was affiliated, respectively.

Table 1: Protocols submitted to ISAC for the first time Apr 2007-Mar 2008

Study type	Number of submissions	Percentage of total
Disease epidemiology only	33	28.9
Adverse drug reactions	32	28.1
Drug use only	17	14.9
Drug effectiveness	8	7.0
Disease epidemiology & drug use	4	3.5
Pharmacoeconomics	3	2.6
Other	17	14.9
Total	114	100%

- 4.2.2. Table 2: Protocols submitted to ISAC for the first time in Apr 2007-Mar 2008, by type of organisation to which the study's principal investigator was affiliated

Organisation Type	Number of submissions	Percentage of total
Academia	61	53.5
Pharmaceutical Industry	24	21.1
Research Services Provider	6	5.3
Government	15	13.2
Academia & Pharmaceutical	3	2.6
Academia & NHS	2	1.7
NHS	2	1.7
Other	1	0.9
Total	114	100%

- 4.2.3. Table 3 gives a breakdown of the 114 first-time submissions from Apr 2007-Mar 2008 by the recommendation made by ISAC.

Table 3: Protocols submitted to ISAC for the first time in Apr 2007-Mar 2008, by outcome of ISAC initial review

ISAC recommendation	Number of protocols	Percentage of total
Accepted	4	3.5
Accepted with comments	36	31.6
Revision requested	67	58.8
Rejected	7	6.1
Total	114	100%

- 4.2.4. Table 4 details the time taken for GPRD submissions to be processed by ISAC.

Table 4: Elapsed time (in days) between receipt of protocols and questionnaires by ISAC secretariat and dispatch of initial ISAC evaluation to applicant Apr 2007-Mar 2008 (excluding weekends)

Number of submissions	Median	Range (min-max)	Mean \pm SD
114	16	3-38	16 \pm 5

4.2.5. The MRC Scheme

In November 2005, the UK MRC finalised agreements with the GPRD to fund access for up to 50 datasets per year for 5 years, for UK academics.

The analysis presented below is for the **36** submissions considered during the period Apr 07 – Mar 2008. Tables 5 and 6 below, shows a breakdown of these protocols by study type and reviewing outcomes.

4.2.6. Table 5: MRC Protocols submitted to ISAC for the first time in Apr 2007-Mar 2008, by study type

Study type	Number of submissions	Percentage of total
Disease epidemiology only	13	36.1
Adverse drug reactions	7	19.4
Drug use only	5	13.8
Drug effectiveness	3	8.3
Pharmacoeconomics	0	0
Disease Epidemiology & drug use	1	2.7
Other	7	19.4
Total	36	100%

4.2.7. Table 6: MRC Protocols submitted to ISAC for the first time in Apr 2007-Mar 2008, by outcome of ISAC initial review

ISAC recommendation	Number of protocols	Percentage of total
Accepted	0	0
Accepted with comments	9	25
Revision requested	23	63.8
Rejected	4	11.2
Total	36	100%

4.2.8. Publications

The findings of a number of studies approved by ISAC were published as research papers in international journals. A comprehensive list of publications based on data from the GPRD is available from the GPRD website:

<http://www.gprd.com/info/bibliography.asp>

5. Background to work of the MHRA

The Medicines and Healthcare products Regulatory Agency (MHRA) is an executive agency of the Department of Health. Its role is to protect and promote public health and patient safety by ensuring that medicines, healthcare products and medical equipment meet appropriate standards of safety, quality, performance and effectiveness, and that they are used safely. The MHRA is the data controller of two unique and nationally important databases that contain patient data: the GPRD and the Yellow Card database.

5.1. Background on Yellow Card Data

5.1.1. The MHRA's Pharmacovigilance role

Under the Medicines Act, the Commission on Human Medicines (CHM) gives advice to the Licensing Authority (MHRA acting on behalf of the Secretary of State for Health) on the safety, quality or efficacy of medicines and for promoting the collection and investigation of information relating to adverse drug reactions (ADRs). ADRs in the UK are reported through the UK's Spontaneous ADR Reporting Scheme (the Yellow Card Scheme). The Scheme is voluntary for health professionals and patients, whereas pharmaceutical companies are legally obliged to report serious ADRs to the MHRA. This scheme was set up in 1964 and since then, more than 500,000 UK reports have been received. Approximately 18,000 UK reports of suspected ADRs are received every year.

The Vigilance and Risk Management (VRMM) division of MHRA is responsible for identifying signals of possible drug-safety hazards from this information, investigating these, and where necessary, conducting risk-benefit analyses to determine whether any action is necessary to minimise risk. Issues of drug safety may also be brought to the attention of the MHRA from many other sources, and are similarly investigated and acted upon.

Information obtained from post-marketing experience may lead to the need for the Marketing Authorisation to be updated in variety of ways. This leads to amendment of the Summary of Product Characteristics (SPC), which range from restriction of the indication, addition of contraindications or warnings, addition of monitoring requirements or addition to the list of recognised side effects. All changes made to the SPC are reflected in the Patient Information Leaflet that accompanies the medicine.

5.1.2. The Independent Review of Access to the Yellow Card scheme

The Review was instigated to respond to the increasing number of requests from individuals and organisations outside the MHRA for access to the Yellow Card database. The Review was conducted by HM Inspector of Anatomy Dr Jeremy Metters, included a 24-week public consultation period and the 24 main recommendations were published in 2004.²

2

http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON024
108

In January 2005, the Government responded to recommendations of the *Report of an Independent Review of Access to the Yellow Card Scheme* about opening access to Yellow Card Scheme data, together with other recommendations on enhancing the operation of the Yellow Card Scheme.

The Independent Review strongly encouraged the MHRA to make Yellow Card data more widely available, especially to facilitate public health research, and suggested that applications for data should be reviewed by a committee independent of the MHRA prior to consideration by an ethics committee.

5.1.3. The Interim Committee on Yellow Card Data

With the agreement of the MHRA Board, a time-limited interim advisory committee on the release of Yellow Card data was created. Chaired by Dr Jeremy Metters, the committee met 4 times between April 2005 and July 2005 with the following terms of reference:

- Advise on development of arrangements for release of Yellow Card data;
- Advise on protocols and procedures for a permanent committee; and
- Consider pre-existing requests for data, within limitations.

The Committee developed an application form and process for reviewing Yellow Card data ahead of a permanent committee (the ISAC) being established.

5.2. Background on the General Practice Research Database

The General Practice Research Database (GPRD) is a database of anonymised longitudinal health records collected from primary care (general practices) across the United Kingdom. The database currently contains data for almost 3 million active patients (9 million patients ever) from over 400 UK practices. The database is managed by the GPRD Group at the MHRA on behalf of the Secretary of State for Health. Data from the GPRD are made available to researchers for public health research purposes only, on a nonprofit making basis.

The GPRD has been used extensively for research in areas such as clinical epidemiology, drug safety, and health outcomes. Due to the nature of the data held in GPRD, research involving these data is most often observational data subject research³. Since its inception, in excess of 480 research papers based on GPRD data have been published.

5.2.1. History

The GPRD was established in June 1987 as the VAMP Research Databank. At this time, participating GPs received practice computers and the VAMP Medical, text-based practice management

³ Data subject research: A data subject is a term used to denote person specific data held in an anonymous format that has been collected without any intervention on a human subject other than that in normal clinical care from which the data emanates.

system in return for undertaking data-quality training and submitting anonymised patient data for research purposes. The number of practices participating in this arrangement grew rapidly, and the first research studies using GPRD were published during the early 1990s.

In November 1993, Reuters Health Information acquired VAMP Ltd. In 1994, Reuters decided to donate the database to the Department of Health, whilst it continued its interest in the provision of practice management software. The database was renamed GPRD at this time. The database was donated to the Department on the condition that the database could be used only for medical or health research on a nonprofit making basis; these conditions were defined in the Asset Transfer Deed which effected the transfer of the database to the Department.

In 1995, Reuters launched Vision, a major new Windows-based practice management software application, which has become the only practice software used by GPs in the GPRD scheme. In 1999, Reuters' practice management software business was acquired by Cegedim, a European healthcare software and research company, and renamed In Practice Systems.

Since 1994 the Secretary of State for Health has owned the database, and between 1994 and 1999 the database was managed by the Department's Statistics Division and operated by the Office for National Statistics (ONS). In 1999, the Medicines Control Agency - MCA (which became part of the newly created MHRA in April 2003) took over management of the GPRD. At this time, GPRD's operations were relocated from ONS to the MCA and a major redevelopment programme initiated to enable broader research usage of the data both within the UK and overseas.

5.2.2. The GPRD Group

The GPRD Group is the team within the MHRA responsible for all aspects of the operation and management of the GPRD. It comprises a multi-disciplinary team of around 25 staff, led by Dr John Parkinson, who has extensive experience managing anonymised patient databases (10 years MEMO, Tayside, University of Dundee, prior to GPRD).

The GPRD Research Team, which currently comprises 9 staff, including epidemiologists and statisticians, is headed by Dr Tjeerd van Staa who has extensive experience in pharmacovigilance and epidemiology, and has published widely on research using GPRD data.

The GPRD Group aims to maximise the use of the GPRD to support public health research, both in the UK and internationally, based

upon the research utility of this key dataset whilst protecting the confidentiality of patients, contributing general practitioners and adhering to UK and European data protection legislation, under robust research governance arrangements.

5.2.3. Data

The GPRD currently collects data from over 400 general practices across the United Kingdom. As of October 2006, the number of currently registered ('active') individuals in the GPRD is around 3.23 million, representing approximately 5% of the population of the United Kingdom; in total, 5.91 million individuals are represented in the database.

The GPRD Group collects data from practices including the entire medical record, with the exception of strong patient identifiers (e.g. name, address, date of birth, NHS number). Information collected includes demographic information (including age and sex), medical symptoms, signs and diagnoses, therapy, referrals to hospitals or specialists, laboratory tests and pathology results, lifestyle factors (e.g. height, weight, BMI, smoking and alcohol consumption) and patient registration details.

The current standard practice for the use of such anonymised data is adopted by GPRD and research done under implied consent. However, GPRD works with contributing practices to ensure patients are aware of such use of their data and of their right to opt out if they so wish. All patient records are collected from a contributing practice except where individual patients have exercised their right to opt out of contributing to the GPRD.

5.2.4. Data Collection

Data are collected from contributing practices which use the Vision Clinical System software provided by In Practice Systems Ltd. On acceptance as a GPRD contributor, a Full Data Collection (FDC) is taken from the practice computer followed by Incremental Data Collections (IDCs).

The software required to carry out the data collection process is an integral part of the Vision practice software system. Initialisation of the process is by means of a floppy disc, tape or electronic transfer over NHSnet for every collection request and contains the required details for every collection (Collection type, audit sequence number for collection start, etc.) Practice staff initiate the collection, check the data if they wish, back it up to media, and return it to the GPRD Group.

Upon return, the data are extracted from the collection media and are verified for integrity and completeness before further processing. If a collection fails these checks a re-collection is requested.

Updates are made via Incremental Data Collections (IDCs) extracted at the practice and any new patients which have been registered since the previous collection. IDCs are requested on a six to eight week cycle, subject to the practice carrying out their collections in a timely manner, the collection being acceptable quality and the collection file passing the technical integrity checks.

The MHRA has a contract with In Practice Systems to ensure that GPRD data collection contains uninterrupted in the event of upgrades to the Vision software.

5.2.5. Anonymisation

In order to be able to update individual longitudinal patient records on an ongoing basis, it is important that every patient and practice within the database can be distinguished uniquely, so that new information about a specific patient at a specific practice can be added to the appropriate longitudinal record. Privacy-enhancing technology is used to achieve this without the need to collect information such as names, addresses and NHS numbers. This ensures that the identity of individuals within the database cannot be established by anyone within the GPRD Group or by researchers using GPRD data.

During the process of data collection, the collection software identifies the practice using the In Practice Systems User Number. The collection software does not collect any other practice identifiers. The collection software also encrypts the identity numbers of doctors and other practice staff who enter data into their system. At the time of registration, the practice computer allocates a unique identifier to every patient. This identifier is used by the practice system to allocate later data to the same patient file. The collection software does not collect the data fields of the patients which contain personal identifiers (e.g. title, name, address, postcode etc).

As an additional precaution, the patient identifier and practice number are encrypted for a second time prior to being made available to researchers via the GPRD data warehouse.

5.2.6. Free text fields

GPs are able to type information into 'free text' fields in Vision: the information they can enter is not restricted and so may contain information that identifies the patient. GPs can prevent the collection of individual free text fields (for instance, if it contains patient identifiers) by entering a double backslash (\\) at the beginning of any text field, but this is only effective if this is done prior to entering any other text in the field.

The free text information included in the comments field is often critical to researchers because these notes provide additional

information about medical conditions. This might include information that can otherwise not be recorded in the main medical record because there is no specific Read code⁴ (e.g. for rhabdomyolysis or for histology results, or information that clarifies or negates a Read code, e.g. myocardial infarction – excluded). Free text notes have been used to verify or to detect clinical outcomes, thus adding to the quality of the research conducted using GPRD.

Although the Recording Guidelines for Vision Users (issued by the GPRD Group to all contributing practices) address the issue of patient confidentiality, and give information on how GPs can ensure that the collection software extracts only free text that does not include potential patient identifiers, their compliance with these methods cannot be guaranteed. Since it is not currently possible to manually anonymise all data as they come in, all free text as collected from practices is simply not released to researchers.

An exception to this is the specific 'dosage instructions' free text field, which has been made available in the GPRD Data Warehouse, following an exercise to remove patient identifiable information from around 35,000 distinct free text phrases (accounting for around 96% of all entries in the dosage instructions field). For the remaining 4%, the 'raw' free text has been replaced with the wording "Anonymised by GPRD".

For free text other than the 'dosage instructions', the GPRD Group provides an anonymisation service, which allows researchers to receive anonymised free text fields for patients/events of interest. The anonymisation of text is carried out by staff in the GPRD Operations Team under the terms of a Standard Operating Procedure previously approved by the Scientific and Ethical Advisory Group (SEAG)⁵. The GPRD Research Team access free text in the same way as any other researcher: i.e. after anonymisation of the text by the GPRD Operations Team.

5.2.7. Using GPRD data for public health research

The GPRD is used for pharmaco-epidemiological and public health research internationally by academic institutions, regulatory agencies, government and health service researchers and research staff in the pharmaceutical industry. Research using GPRD data has traditionally focussed on clinical epidemiology and drug safety/pharmacoepidemiology; however, other uses of the data (e.g. drug utilisation, treatment patterns, health outcomes, pharmaco-economics and health service planning) are becoming

⁴ All clinical terms recorded in patient records are coded using Read Clinical Terms (also known as Read Codes); this terminology is mandatory for the recording of clinical information via National Health Service – approved GP computer systems in the UK.

⁵ SEAG was the independent group responsible for the scientific and ethical review of protocols for research using GPRD data until February 2006, when it was replaced by the Independent Scientific Advisory Committee for MHRA database research

more common. Since 1988, in excess of 480 research papers have been published in a wide variety of peer reviewed scientific journals, illustrating the broad scope of the research for which these data are relevant. These include studies which have contributed to the body of available evidence for high-profile public health issues such as MMR vaccine and autism, and selective serotonin reuptake inhibitors (SSRIs) and self-harm/suicide.

Annex 1 - Membership and member biographies

Professor Jennifer Adgey (Chairman): ^{*} Hon Prof Cardiology Queens University & Hon consultant cardiology, Royal Victoria Hospital, Belfast.

Professor Jackie Cassell: Professor of Primary Care Epidemiology, Honorary Consultant in Health Protection and in Genitourinary Medicine, Brighton and Sussex Medical School

Professor Corinne De Vries: Professor of Pharmacoepidemiology, Department of Pharmacy and Pharmacology, University of Bath

Professor Richard Donnelly: Associate Dean & Professor of Vascular Medicine, University of Nottingham Medical School

Professor Martin Gulliford: Professor in Public Health at King's College London

Professor Amrit (Pali) Hungin: GP, Professor of Primary Care and General Practice and Dean of Medicine and Head of School of Health at the University of Durham.

Dr Umesh Kadam: ^{*} GP Epidemiologist, Research Institute for Primary Care and Health Sciences at Keele University

Professor Paul Little: GP and Prof of Primary Care Research at the Aldermoor Health Centre, Southampton University.

Dr David Lovell: Reader in Medical Statistics, University of Surrey

Dr Richard Martin: Reader in Clinical Epidemiology, Department of Social Medicine, University of Bristol

Ms Barbara Meredith: (lay member)

Dr Sarah Meredith (Deputy Chair): Medical Research Council (MRC) Clinical Trials Unit

Dr Simon Mitchell: ^{*} Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Ms Marcia Saunders: lay member and lay member of the Royal Pharmaceutical Society of Great Britain

Dr Ruben Thanacoody: ^{*} Consultant Physician and Clinical Toxicologist Yellow Card Centre (Scotland) and NPIS (Edinburgh Unit) Royal Infirmary Edinburgh

^{*} Member appointed January 2008

Members who resigned during the year

Dr Brian Gennery : Former Head and Dean of Medicine of the Postgraduate Medical School at the University of Surrey

Guest members who attended during the year

May 2007 – Prof Munir Pirmohamed, Head YCC Mersey

July 2007 – Prof Phil Routledge, Head YCC Wales

Guest speakers who attended during the year

May 2007 – Prof David Hand, Imperial College London

Member biographies

Professor Jennifer Adgey (Chairman) is a honorary consultant cardiologist and honorary professor cardiology at the Regional Medical Cardiology Centre Royal Victoria Hospital Belfast. Her major research interest is pre-hospital coronary care involving myocardial infarction, acute coronary syndromes and cardiac arrest. She is a member of several international steering committees involving studies in acute myocardial infarction and acute coronary syndromes. She sits on the editorial boards of several cardiology journals

Professor Jackie Cassell: Professor of Primary Care Epidemiology, Honorary Consultant in Health Protection and in Genitourinary Medicine, Brighton and Sussex Medical School. She was previously a Senior Clinical Research Fellow at University College London. Jackie leads a programme of health services research in the field of sexually transmitted infections in HIV, and is interested in broadening the public health uses of primary care databases.

Professor Corinne De Vries is Professor of Pharmacoepidemiology at the University of Bath in the UK. She trained as a pharmacist and an epidemiologist and has worked with many of the European databases that are used in pharmacoepidemiology. She is also Vice President with special responsibility for Finance of the International Society for Pharmacoepidemiology (ISPE). Her main areas of interest are drug safety in populations that are excluded from clinical trials such as pregnant women, children, the very elderly and those with multiple comorbidities. Recent research projects cover the disease areas of diabetes, heart disease, endometriosis and a range of autoimmune diseases such as Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis (RA).

Professor Richard Donnelly is Professor of Vascular Medicine and Head of the School of Graduate-Entry Medicine & Health in the University of Nottingham. After graduating in Medicine from Birmingham, his clinical academic career has included posts in the University of Glasgow, Stanford University, California (BHF International Fellow, 1992-4), and the University of Sydney. His clinical & research interests are in cardiovascular endocrinology and therapeutics, especially the vascular complications of diabetes. He is editor of *Diabetes, Obesity & Metabolism*, and; a member of the Clinical Advisory Group on Stroke Prevention for the UK Stroke Research Network; and a Member of the Commission on Human Medicines' Expert Advisory Group on Cardiovascular, Diabetes & Renal products.

Professor Martin Gulliford is Professor of Public Health at King's College London. He is active in GPRD-based research and is interested in the design and analysis of studies with clustered data, access to health care and diabetes care.

Professor Amrit (Pali) Hungin is the Dean of Medicine and Professor of Primary Care and General Practice at the University of Durham. His research interests include therapeutics, the early detection and effective, evidence-based management of disease, particularly in gastroenterology and cardiovascular medicine. He has researched on the management of upper and lower gastrointestinal disorders, including reflux disease and associations with *H pylori*.

He has also published on the epidemiology of gastrointestinal disorders with particular reference to primary care and quality of life issues. Professor Hungin is a founding member of the UK and European primary Care Societies for Gastroenterology, previous Chair of the NHS Research and Development Forum, external examiner to several European and Asian universities and an external advisor to the Italian Medicines Agency (AIFA).

Dr Umesh Kadam is Senior Lecturer in General Practice/Epidemiology at the Research Institute for Primary Care and Health Sciences, Keele University. He is research active in the field of musculoskeletal disorders, comorbidity and ageing, and has a particular interest in using general practice databases and linkage methods for characterising the course of diseases and common symptoms in primary care.

Professor Paul Little is a part time GP at Nightingale surgery in Romsey Hampshire, and Professor of Primary Care Research at the University of Southampton. His particular research interests are in the self help, the management of common illnesses, and health promotion. He has been an advisor to NICE on several guidelines and technology appraisals, serves on the MRC Health Services and Public Health Research Board and the National Institute for Health Research (NIHR) Programme Board.

Dr David Lovell is Reader in Medical Statistics in the Postgraduate Medical School at the University of Surrey at Guildford. Before joining the University of Surrey, David worked for the pharmaceutical company, Pfizer, the toxicology research association, BIBRA International and the Medical Research Council. He is particularly interested in the application of statistical methods to biological problems especially in the area of genetics. He is also a member of the UK Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) and the University of Surrey's Ethics Committee.

Dr Richard Martin is Reader in Clinical Epidemiology, Department of Social Medicine, University of Bristol and Honorary Consultant in Public Health at North Bristol NHS Trust. He is also a member of the National Cancer Research Institute (NCRI) Prostate Clinical Studies Group. He has a longstanding interest in pharmacoepidemiology and the research potential of automated general practice databases, first developed as an academic general practitioner in London and Southampton.

Ms Barbara Meredith is a part-time project manager in the Patient and Public Involvement Programme at the National Institute for Health and Clinical Excellence. She has many years' experience of policy development and user involvement in the fields of ageing and consumer health issues. She is a member of the Patient Information Advisory Group, and serves on the Trustee Board of her local Citizens Advice Bureau.

Dr Sarah Meredith is Head of Clinical Operations at the Medical Research Council Clinical Trials Unit, Honorary Senior Lecturer in the Department of Primary Care and Population Sciences at University College London and Honorary Consultant in Public Health at Redbridge Primary Care Trust. Her

research is mainly in the field of chronic disease prevention, and the assessment of risks and benefits of treatments.

Dr Simon Mitchell is a consultant neonatal paediatrician at St Mary's Hospital, Manchester. His research interests include genetic factors in the aetiology of cerebral palsy, dosage & administration of neonatal vitamin K prophylaxis and the clinical effects of intrauterine growth restriction. He is a member of the British Paediatric Surveillance Unit Executive Committee, Central Manchester Research Ethics Committee and Health Technologies Appraisals Committee at the National Institute for Health & Clinical Excellence.

Ms Marcia Saunders is Chair of Brent Primary Care Trust (Teaching) and was previously Chair of North Central London Strategic Health Authority. Having a special interest in regulation, she is a lay member of the Royal Pharmaceutical Society of Great Britain and an assessor for the General Medical Council's performance procedures. She holds degrees from the University of Bristol, University of Chicago and Cornell University in the USA. She is an elected Fellow of the Faculty of Public Health, Royal College of Physicians.

Dr Ruben Thanacoody is Consultant Physician and Clinical Toxicologist in the Edinburgh Royal Infirmary. He has a longstanding interest in pharmacovigilance and is involved in Yellow Card Centre (Scotland). His research interests include drug-induced QT prolongation and adverse reactions to acetylcysteine.

Annex 2 Duties of members

- Provide formal and informal advice to MHRA between meetings. Applications will be circulated electronically to ensure they are reviewed within 20 days and most GPRD applications will have to be decided without committee members meeting in person.
- Attend all scheduled and unscheduled meetings of the Committee.
- Consider, comment and contribute by their individual expertise and judgement as appropriate on all agenda items and to assist the Committee to frame clear and unequivocal advice to MHRA in accordance with the Committee's terms of reference.
- Be able and be prepared to speak on a range of relevant issues and not just their own areas of specialism.
- Develop an understanding of the types and uses of data contained in the GPRD and Yellow Card databases and understand how and when release of data (in particular Yellow Card data) could lead to patients being identified if applications are not robust scientifically.
- Possess or develop an understanding of the UK/European medicines regulatory procedures.

Annex 3 Fundamental principles of the Yellow Card Scheme

Sir Derrick Dunlop, who was Chairman of the Committee on Safety of Drugs (CSD) when the Yellow Card Scheme was launched in 1964, set out five basic principles which have stood the test of time.

- A voluntary scheme based on the good will of reporters
- The collation of reports of ADRs without a causal link needing to be established
- Reporters are encouraged to report without delay
- All reports are held in complete confidence by the MHRA and CSM
- The data are never to be used for disciplinary purposes or for enquiries about prescribing cost

Annex 4 Glossary of acronyms

ADR	Adverse drug reaction
CSM	Committee on Safety of Medicines (replaced in 2005 by CHM)
CHM	Commission on Human Medicines
COREC	Central Office of NHS Research Ethics Committees
DPA	Data Protection Act 1998
FOIA	Freedom of Information Act 2000
GP	General Practice
GPRD	General Practice Research Database
ISAC	Independent Scientific Advisory Committee for MHRA database research
ISPE	International Society for Pharmacoepidemiology
IT	Information Technology
MREC	Multi-centre NHS Research Ethic Committee
MRC	Medical Research Council
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NRR	National Research Register
REC	NHS Research Ethics Committee
RCPCH	Royal College of Paediatrics and Child Health
SEAG	Scientific and Ethical Advisory Group
SPC	Summary of Product Characteristics
UK	United Kingdom
VRMM	Vigilance and Risk Management division of MHRA (formerly Post Licensing Division)
YCC	Yellow Card Centre

ANNEX 5 Declaration of interests

MEMBERSHIP OF THE INDEPENDENT SCIENTIFIC ADVISORY COMMITTEE (ISAC)

MEMBERS HAVE DECLARED CURRENT PERSONAL AND NON-PERSONAL INTERESTS AS FOLLOWS

	PERSONAL INTERESTS		NON PERSONAL INTERESTS		
MEMBER	NAME OF COMPANY	NATURE OF INTEREST	NAME OF COMPANY	NATURE OF INTEREST	WHETHER CURRENT
Prof Jennifer Adgey	Merck, Sharp & Dohme Boehringer Ingelheim Bristol Myers Squibb GlaxoSmithKline Servier Boehringer Ingelheim Eli Lilly	Consultancy Consultancy Lecture Share holdings Travel expenses international meetings Travel expenses international meetings Travel expenses international meetings	Sanofi Aventis	Research Grant	Yes
Prof Jacqueline Cassell	None				
Prof Corinne de Vries	None		Novo Nordisk GSK Pharma GSK Bio Schering AG Organon NV Wyeth BUPA Healthcare Commission	Research grant Expert services re: pregnancy study Research grant re: autoimmune disease Research Grant re: CPA Research grant re: livial Studentship re: HRT Research Grant re: endometriosis Research grant re: NSF in CHD	No Yes Yes No No Yes Yes No

	PERSONAL INTERESTS		NON PERSONAL INTERESTS		
MEMBER	NAME OF COMPANY	NATURE OF INTEREST	NAME OF COMPANY	NATURE OF INTEREST	WHETHER CURRENT
Prof Richard Donnelly	Takeda UK Servier Laboratories UK	Consultancy (diabetes & cardiovascular) Consultancy (diabetes & cardiovascular)	None		
Dr Brian Gennery	Eli Lilly Arakis Point Bio Cambridge Pharma PharmaKodex GlaxoSmithKline	Shares Consultancy Consultancy Consultancy Consultancy Air fare to India	Sanofi Merck Pfizer GlaxoSmithKline Sepracor Esai	Clinical trials in unit Clinical trials in unit Clinical trials in unit Clinical trials in unit Clinical trials in unit Clinical trials in unit	Yes Yes Yes Yes Yes Yes
Dr Martin Gulliford	None		None		
Prof Amrit (Pali) Hungin	GlaxoSmithKline Red Door Consultancy Reckitt Benkiser Proctor & Gamble Novartis	Consultancy (for constipation therapies) Consultancy (Rotavirus vaccination) Consultancy (Gastro-oesophageal reflux disease) Research grant, travel and accommodation to professional meetings (Inflammatory Bowel Disease) Consultancy (Irritable Bowel Syndrome)	Proctor & Gamble Wyeth Abbott Novartis	Research grant (inflammatory bowel disease) Research grant (reflux disease) Research grant (H pylori infection) Research grant (irritable bowel syndrome)	Yes No No Yes

	PERSONAL INTERESTS		NON PERSONAL INTERESTS		
MEMBER	NAME OF COMPANY	NATURE OF INTEREST	NAME OF COMPANY	NATURE OF INTEREST	WHETHER CURRENT
Dr Umesh Kadam	None		None		
Prof Paul Little	Abbott Pharmaceuticals	Consultancy (two half day sessions on the complications of respiratory tract infections)	None		
Dr David Lovell	Pfizer AstraZeneca	Shares, stock options, member of pension scheme Spouse owns shares	Emergent Bio Solutions	Member of safety monitoring committee	Yes
Dr Richard Martin	None		None		
Ms Barbara Meredith	None		None		
Dr Sarah Meredith	Bayer	Donation of drugs for a trial of new regimens for tuberculosis in Africa (REMox TB trial funded by EDCTP)	None		
Dr Simon Mitchell	Trinity Pharmaceuticals (Curosurf surfactant – marketed by Chiesi Ltd)	Grant to support attendance at academic meeting in Washington DC – total value £300 (paid air fare). Received Oct 07, meeting attended Dec 07	None		

	PERSONAL INTERESTS		NON PERSONAL INTERESTS		
MEMBER	NAME OF COMPANY	NATURE OF INTEREST	NAME OF COMPANY	NATURE OF INTEREST	WHETHER CURRENT
Ms Marcia Saunders	None		None		
Dr Ruben Thanacoody	None		None		

Annex 6 - ISAC Appeal process

If the MHRA accepts the advice of ISAC to turn down an application for data, the unsuccessful applicant will be sent a letter setting out the reasons why. The applicant will be told that he/she has 28 days from the date of the letter to make representations, and that these should be made in writing to the YellowCard/GPRD ISAC Secretary as appropriate. The applicant will be informed that once this 28 day period has expired, he/she will have to make a fresh application. If an appeal is to be carried out then the Licensing Authority will appoint a person or persons to undertake a review of the documentation. A letter will be sent to the applicant with the outcome of the appeal. The decision of the Licensing Authority will be final.