

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

(ISAC)

Annual Report
February 2006-March 2007

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Foreword from the Chairman of the MHRA

In recent years, the Medicines and Healthcare products Regulatory Agency (MHRA) has been striving to become more open and improve relations with our external stakeholders, including the public, industry and the academic community. This has been due in part to legislation such as the Freedom of Information Act, but is also illustrative of our desire to provide a professional and efficient customer service. Although General Practice Research Database data have been available for some time, opening up access to the Yellow Card database was a new venture, and yet another milestone in implementing the recommendations of the *Independent Review of Access to Yellow Card data*.

This first year of the Independent Scientific Advisory Committee for MHRA database research (ISAC)'s operation has seen two rounds of members being appointed by the Appointments Commission and the establishment of a new Committee that replaces the former Scientific and Ethical Advisory Group for the GPRD and the Interim Committee on Yellow Card data. I am pleased that we have been able to attract membership from a range of academic and professional backgrounds coupled with strong lay representation to ensure that every application is robustly reviewed.

Increasing amounts of data are stored on databases in the UK and throughout Europe, prompting much media interest about reuse of government data. In this climate the importance of rigorous scientific review to safeguard MHRA data has never been more important and I am pleased that the excellent progress the ISAC has made in its first year will ensure the appropriate release of Yellow Card and GPRD data for many years to come.

I would like to conclude by thanking Dr Brian Gennery for chairing the ISAC during its first year, to pay tribute to the health professionals whose altruism in reporting provides the lifeblood of the Yellow Card scheme, and also to thank the GP practices who continue to supply data to the GPRD. Without the partnership that we have with those who provide our data none of the valuable research approved by ISAC would be possible.

Professor Sir Alasdair Breckenridge
MHRA Chairman
June 2007

Foreword from the Chairman of the ISAC

Welcome to the first Annual Report of the Independent Scientific Advisory Committee for MHRA database research (ISAC), covering the period February 2006 to March 2007.

The ISAC was founded to enable the use of MHRA data for public health research whilst protecting the identity and interests of those who have provided the data in confidence. The ISAC ensures that the integrity and reputation of the Yellow Card database and General Practice Research Database are upheld, and the first year has seen the review of many challenging and exciting protocols. Topics covered have included genetics, research into long-term conditions, cancer, drug safety and epidemiology. These are illustrative of the wealth of data contained in these two important MHRA databases.

The introduction of the Medical Research Council licence, which provides access for up to 50 GPRD datasets per year for UK academics, has been important in opening up the GPRD to a wider audience. I am also pleased that applications for Yellow Card data have been received from a variety of different applicants, both large organisations and individual researchers. It is important that ISAC data are widely accessible to benefit public health research, and the initial feedback we have received from applicants and their enthusiasm to access data has been encouraging.

The consideration of how issues such as patient identity, consent and ethics could be addressed was an important topic we considered in the first year. I am very pleased that we were able to agree with the Central Office of Research Ethics Committees (RECs) that ethical approval of ISAC applications would be carried out by NHS RECs, to ensure separate scientific and ethical review in line with current best practice for research governance.

The first phase in the life of the ISAC has been to establish an effective review process and continue the high level of review operated by its predecessors. The next phase will be to keep abreast of the many changes taking place in UK health research and strengthen links with other research bodies so that the ISAC continues to follow best practice. I am sure that with such strong professional and lay membership the ISAC will overcome any future challenges and would like to thank all members for their dedication over the past year.

Dr Brian Gennery
ISAC Chairman
June 2007

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 ten professional ISAC members, chaired by Dr Brian Gennery, with expertise in statistics, epidemiology, general practice and clinical pharmacology. There are also two lay members. Since July 2006, one of the Heads of the five regional MHRA Yellow Card Centres (YCCs) has been invited to attend every meeting as a guest member with expertise in the Yellow Card Scheme. Full information on membership is included at Annex 1.

Due to the high volume of work, the Committee currently 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 first year

2.1. Outputs

- The new Committee met five times and reviewed a total of 127 GPRD protocols and 4 Yellow Card applications for the first time. (see *Chapter.5*)
- Reviewed 39 Medical Research Council (MRC) applications under the new initiative.
- Approved for the first time the release of Yellow Card data where contact with patients will be required.
- Advised MHRA on the development of *Guidelines for Safe Disposal of Electronic Yellow Card Data for External Users* to ensure applicants handle, store, transmit and destroy data securely.

2.2. Highlights of the first year's meetings

The five meetings held in the period covered by the first annual report were on Tuesday 28 February 2006, Wednesday 10 May 2006, Monday 17 July 2006, Wednesday 29 November 2006 and Friday 16 February 2007. Summary minutes of all these meetings have been published on the MHRA website.¹ The first meeting was an induction for members, and the first part of the meeting on 29 November 2006 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 first year are outlined below.

2.2.1. Patient involvement and ethical issues

Issues around patient involvement in research were considered by the Committee at every meeting. Ethical approval through a NHS Research Ethics Committee following ISAC scientific approval is a requirement for Yellow Card applications where contact with patients or reporters is desired.

In July 2006, GPRD obtained MREC approval to cover observational research using the database. This, however, does not cover research in which direct patient involvement is necessary or where GPRD data is to be linked to patient identifiable information from another source. In situations where this might be applicable, applicants are asked by ISAC to seek separate ethical approval from the relevant Research Ethics Committee before the study can be approved to use GPRD data.

Where a researcher wished to contact the subject of a Yellow Card report, the MHRA insists that initial contact with Yellow Card reporters or patients is made by the MHRA as the data holder of Yellow Card data under the DPA. Data protection requires that personal details are not given to third parties without the data provider's consent. At the time of writing, two

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

Yellow Card applications have been approved by ISAC where contact with patients is required. The MHRA is developing standard letters and procedures for contacting them. Once initial contact with a patient or reporter has been made by the MHRA and they have consented to participate in research, researchers will be permitted to contact patients directly.

2.2.2. The National Research Register

Following a suggestion made at the first ISAC meeting, the ISAC endorsed proposals for the contribution of information on ISAC-approved protocols to the National Research Register (NRR), which is a register of ongoing/recently completed research projects funded by, or of interest to, the NHS. This is to ensure that the wider research community is aware of ISAC-approved research and to facilitate academic collaboration. The following form of words for inclusion in ISAC guidance was agreed:

The National Research Register (NRR) is a register of ongoing and recently completed projects funded by, or of interest to, the UK National Health Service.

*ISAC **strongly** recommends that UK researchers using GPRD consider registering as NRR data providers, in order that others engaged in research within the UK can be made aware of current works.*

*Registration with the NRR is **entirely voluntary** and will not replace information on ISAC approved protocols published in summary minutes or in the ISAC Annual Report.*

2.2.3. IT security and confidentiality of ISAC data

The Committee discussed a number of issues in relation to IT security to ensure that the confidentiality of patients whose data are stored on MHRA databases is protected and, in the case of Yellow Cards, that the reporter's identity is also protected.

Applicants must state on the GPRD and Yellow Card application forms how they will comply with IT security requirements imposed by ISAC. To assist Yellow Card researchers, IT security guidelines were published in February 2007 on how successful researchers must store, handle, transmit and destroy Yellow Card data. IT security requirements are communicated to all licensed users of GPRD by the inclusion of the relevant clause/s in both the GPRD and MRC licence agreement.

The Committee also considered the security requirements of ISAC members, who receive confidential paperwork on applications ahead of and between meetings. The Committee agreed to pilot using the MHRA Portal for secure transmission of applications between MHRA and Committee members. This pilot is ongoing at the time of writing.

2.2.4. Promotion of Yellow Card data for research

The Committee considered different ways to promote greater awareness of the opening up of the Yellow Card database for research following the 2004 *Independent Review of Access to the Yellow Card Scheme*. The MHRA has established, with the Commission on Human Medicines, a Working Group on Strengthening the Yellow Card Scheme and this work will be taken forward in this context.

3. Lessons learned from the first year

The first year of ISAC's operation has seen a number of high-quality applications approved by the Committee. Successful applicants have paid careful attention to guidance notes and submitted concise applications, with a tightly focussed hypothesis making it clear exactly what data are required and why. MHRA is aware it has taken time for some of the new review processes to become established and is grateful to applicants for the patience and understanding shown during ISAC's first year. It is hoped some of the information below will assist future applicants and ensure a smooth journey through the review process.

3.1. Reasons why Yellow Card applications were rejected by the ISAC and Interim Committee on Yellow Card data

- The research hypothesis was insufficiently specific;
- Reaction terms were not sufficiently defined and it was therefore impossible to extract meaningful data on which scientific conclusions could be drawn from the database;
- A reaction to a drug was already known and the study would not quantify this further;
- Commercial use of Yellow Card data could not be approved as it has been freely and voluntarily supplied for the public good.

3.2. Advice offered to Yellow Card applicants needing to resubmit an application included:

- Provision of detailed information about the statistical approach and ensuring there was a control group;
- Ensuring there were adequate IT security storage and destruction policies in place. The MHRA published guidance in February 2007 on how we expect external users to store Yellow Card data, which must be followed, and to assist applicants;
- A further reminder that if applicants wanted to contact patients as part of a study, following ISAC approval they must gain ethical approval from a NHS Research Ethics Committee before Yellow Card data were released. If the researcher had already obtained ethical approval for the study and wished to incorporate Yellow Card data into this, the applicant could submit a notice of amendment form to the appropriate NHS REC following ISAC scientific approval;
- GPRD studies might be more suitable than a Yellow Card study to test certain hypotheses;
- It is advisable to contact the MHRA before completing and submitting an application form to discuss data requirements. For example, data such as a case series can be provided under the FOIA and ISAC approval is not normally required for these types of data;
- Requests for large amounts of data will be resource intensive for MHRA staff. Although the MHRA can and will charge for release of data, applicants must be aware that much of the work associated with release of data and its validation must be done by MHRA staff and

extra resource cannot simply be brought in to handle a large request for data. Provision of data must not deflect MHRA from its statutory regulatory function and less resource intensive requests will be processed more quickly.

3.3. GPRD Lessons

There was a clear need to standardise the way in which applicants who requested data using the GPRD formulated protocols for consideration by ISAC. Standardisation of both the format and content of research proposals would improve the review process by making it both fairer and more efficient.

The Committee therefore made the decision to update the GPRD ISAC Application form based on the International Society for Pharmacoepidemiology (ISPE) Good Practices. This form was updated in July 2006, and required applicants to include details of the following in all protocols requesting access to data using the GPRD:

- Objectives, aims and rationale
- Background to the study
- Study population including estimate of numbers expected in GPRD
- Selection of comparison groups or controls
- Exposure, outcomes and covariates
- Data analysis
- Limitations of study design and analytical methods and
- Plans for disseminating results

The updated form also requested information on the ability and expertise of researchers to conduct analysis on GPRD or similar data. Applicants were also asked to collaborate with, or to include in their research teams, individuals with some knowledge and experience of UK primary care. This was thought to be essential to inform the formulation and analysis of research as well as to assist with the interpretation of findings.

3.3.1. Protocol blinding

In July 2006, the decision was taken to pilot the blinding of GPRD protocols to evaluate whether the review process could be undertaken more fairly and objectively. Personal identifiable information as well as details relating to applicants affiliation were removed from protocols prior to consideration. The pilot period extended from July 2006 – Jan 2007.

At the end of the period, the decision was taken to discontinue blinding. Many reviewers felt that despite the merits of the blinding process, there were also merits in assessing the capabilities, reputation and experience of applicant's seeking approval to undertake research. Such information, coupled with the scientific and ethical integrity of protocols, could better serve to safeguard public health interests.

Yellow Card applications have never been blinded because the Interim Committee on Yellow Card data and ISAC both considered that it is important to know the background of applicants to help determine why they want Yellow Card data and whether they should be released.

3.3.2. External Consultations

During the year, one of the growing concerns of ISAC centred on the potential for GPRD to attract applicants with an interest in undertaking data mining activities in the database. To help to inform and develop a framework to evaluate possible future applications, ISAC sought initial external expert advice on the science and methodology of data mining.

There will be ongoing work with the GPRD to develop the relevant framework and processes for considering and reviewing data mining requests.

3.3.3. Common problems with GPRD applications

The main issues besetting applications that requested GPRD data during the year were concerned with:

- Failure to communicate approaches to deal with issues of confounding and bias in their study
- Failure to calculate sample size and/or power .
- Limited understanding of the referral mechanism in the UK primary care system and its interface with secondary care.
- Need for greater involvement of people with subject-specific expertise to inform study design methodology.
- lack of appreciation of limitations of clinical data and problems of analysing large datasets.

4. How the ISAC is organised

4.1. 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

4.2. 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.

4.3. 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.

4.4. Costs

Members are entitled to claim a fee for every meeting. Fees payable are:

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

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.

4.5. 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.

4.6. 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.

4.7. 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 will usually be 1 April-31 March, but the first report is from 1 February 2006 to 31 March 2007 because of the date the Committee was established.

4.8. 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.

5. Applications considered by the ISAC in its first year

5.1. Yellow Card

5.1.1. Total number of applications submitted to ISAC for the first time Feb 2006-Mar 2007

4

5.1.2. Number of applications submitted to ISAC for the first time Feb 2006-Mar 2007, by type of organisation to which the study's principal investigator was affiliated

Organisation Type	Number of submissions	Percentage of total
Academia	3	75%
Independent Researcher	1	25 %

5.1.3. Total number of applications approved by ISAC Feb 2006-Mar 2007 (including 2 requests for further information from Interim Committee)

3

5.1.4. Total number of applications rejected by ISAC Feb 2006-Mar 2007

2

5.1.5. Total number of requests for further information requested by ISAC Feb 2006-Mar 2007

1*

5.1.6. Information on applications approved by ISAC Feb 2006-Mar 2007 (including 2 requests for further information from Interim Committee)

Ref	Applicant	Title	Affiliation
AYCD006	Prof Nick Bateman	Acute renal toxicity and its detection by the Yellow card scheme	University of Edinburgh
AYCD007	Prof Munir Pirmohammed	Pharmacogenetics of antimicrobial drug-induced liver injury	University of Liverpool
AYCD009	Dr Mariam Molokhia	European case-control collection of selected ADRs	London School of Hygiene and Tropical medicine

* This case (Ref 012) was later withdrawn by the applicant and data were provided under the provisions of the FOIA

5.1.7. Under the ISAC’s remit to advise MHRA on “wider aspects of the release of Yellow Card data”, the MHRA also asked ISAC to consider Yellow Card Data the MHRA proposed to provide to Yellow Card Centres (formerly Regional Monitoring Centres). In May 2006 ISAC approved the release of images of Yellow Cards to YCCs to follow up incomplete reports on behalf of MHRA, provided they were destroyed once follow up had been completed and that the YCCs abided by MHRA IT security guidelines.

5.1.8. Publications

To date, no research using ISAC-approved Yellow Card data have been published. However, research using Category II data approved by ISAC’s predecessor, the Interim Committee on Yellow Card data, has now been published (*see section 6.1.5*).

5.2. GPRD : Consideration of applications

During the period Feb 2006 – Mar 2007, ISAC considered 127 new protocols, 3 re-submissions previously reviewed under SEAG and 4 questionnaires. The analysis presented below is of the 127 first-time submissions considered during the period Feb 06–Mar 2007. Tables 1 and 2 show a breakdown of these protocols by study type and organisation to which the principal investigator was affiliated, respectively.

5.2.1. Table 1: Protocols submitted to ISAC for the first time Feb 06- Mar 2007, by study type

Study type	Number of submissions	Percentage of total
Disease epidemiology only	59	46.4%
Adverse drug reactions	37	29.1%
Drug use only	9	7.1%
Drug effectiveness	8	6.3%
Disease epidemiology & drug use	2	1.6%
Pharmacoeconomics	4	3.2%
Other	8	6.3%
Total	127	100%

5.2.2. Table 2: Protocols submitted to ISAC for the first time in Feb 06-Mar 2007, by type of organisation to which the study's principal investigator was affiliated

Organisation Type	Number of submissions	Percentage of total
Academia	79	62.2%
Pharmaceutical Industry	22	17.3%
Research Services Provider	4	3.1%
Government	17	13.4%
Academia & Pharmaceutical	1	0.8%
Academia & NHS	2	1.6%
NHS	1	0.8%
Other	1	0.8%
Total	127	100%

5.2.3. Table 3 gives a breakdown of the 127 first-time submissions from Feb 06-Mar 2007 by the recommendation made by ISAC.

Table 3: Protocols submitted to ISAC for the first time in Feb2006-Mar 2007, by outcome of ISAC initial review

ISAC recommendation	Number of protocols	Percentage of total
Accepted	4	3.1%
Accepted with comments	57	44.9%
Revision requested*	64	50.4%
Rejected	2	1.6%
Total	127	100%

5.2.4. 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 Feb 2006-Mar 2007(excluding weekends)

Number of submissions	Median	Range (min-max)	Mean \pm SD
127	14.0	9 - 67	14.4 \pm 6

5.2.5. 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.

During the first year of the scheme (Dec 2005 – Nov 2006), ISAC considered **30** of the 42 applications seeking data under the new arrangement. There were no rejections. During Dec 06 – March 07, ISAC considered a further **10** applications for data under the scheme

The analysis presented below is for the **40** submissions considered during the period Feb 06 – Mar 2007. Tables 5 and 6 show a breakdown of these protocols by study type and outcomes.

5.2.6. Table 5: MRC Protocols submitted to ISAC for the first time in Feb 06–Mar 07, by study type

Study type	Number of submissions	Percentage of total
Disease epidemiology only	23	57.5%
Adverse drug reactions	7	17.5%
Drug use only	1	2.5%
Drug effectiveness	3	7.5%
Pharmacoeconomics	1	2.5%
Disease Epidemiology & drug use	1	2.5%
Other	4	10.0%
Total	40	100%

5.2.7. Table 6: MRC Protocols submitted to ISAC for the first time in Feb 06 – Mar 07, by outcome of ISAC initial review

ISAC recommendation	Number of protocols	Percentage of total
Accepted	2	5%
Accepted with comments	16	40%
Revision requested	20	50%
Rejected	2	5%
Total	40	100%

5.2.8. 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>

6. 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.

6.1. Background on Yellow Card Data

6.1.1. 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.

6.1.2. 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

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.

6.1.3. 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.

6.1.4. Membership of the Interim Committee on Yellow Card Data

Dr Jeremy Metters CB (Chairman)

HM Inspector of Anatomy and former Deputy Chief Medical Officer

Professor Karen Facey

Evidence Based Health Policy Consultant (Statistician)

Ms Barbara Meredith

Lay representative

Dr Jane Richards OBE

Retired General Practitioner.

Professor Phil Routledge

Professor of Clinical Pharmacology and Head of the Department of Pharmacology, Therapeutics and Toxicology, University of Wales College of Medicine

Dr Darren Shickle

Clinical Reader in Public Health Medicine, School of Health and Related Research, University of Sheffield and Honorary Consultant, North Eastern Derbyshire PCT

Dr Richard Tiner

Medical Director of the Association of the British Pharmaceutical Industry (ABPI)

6.1.5. Work of the Interim Committee on Yellow Card data

As some applications for data were received soon after the Independent Review, initial applications were considered by the Interim Committee. Some of these applications were also discussed by the ISAC as further information had been requested from applicants.

Total number of applications submitted to the Interim Committee on Yellow Card data

8

Total number of applications approved by the Interim Committee on Yellow Card data

3

Total number of applications rejected by the Interim Committee on Yellow Card data

2

Total number of applications on which further information from the applicant was requested

3

Number of applications submitted to the Interim Committee on Yellow Card data by type of organisation to which the study's principal investigator was affiliated

Organisation Type	Number submissions	of	Percentage of total	of
Academia	5		62.5%	
Independent Researcher	1		12.5%	
Commercial	1		12.5%	
Government	1		12.5%	

Information on applications approved by the Interim Committee on Yellow Card data

Ref	Applicant	Title	Affiliation
AYCD002	Dr Anita Holdcroft	Anaesthetic pharmacovigilance - factors affecting ADRs	Imperial College, London

AYCD003	Professor Stephen Evans	PRRs for autoimmune disease	London School of Hygiene and Tropical medicine
AYCD008	Prof. R Mann	Practolol DAP study	Independent researcher

Publications

To date, one study using Type II Yellow Card research has been published. This was a study of Drug Analysis Prints from application AYCD008. It was published under the title "A Ranked Presentation of the MHRA/CSM (Medicines & Health Care Regulatory Agency/Committee on Safety of Medicines) Drug Analysis Print (DAP) data on practolol". The paper was published in *Pharmacoepidemiology & Drug Safety* 2005;**14**:705-710.

6.2. 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.

6.2.1. 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 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

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.

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.

6.2.2. 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.

6.2.3. 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.

6.2.4. 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.

6.2.5. 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.

6.2.6. 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.

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.

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.

6.2.7. 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, pharmacoconomics and health service planning) are becoming 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.

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

Annex 1 - Membership and member biographies

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

Dr Jacqueline Cassell#: Senior Lecturer in Epidemiology and Honorary Consultant in Health Protection, Brighton and Sussex Medical School

Dr Corinne De Vries#: Reader at the Postgraduate Medical School and Head of Pharmacoepidemiology, University of Surrey

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.

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

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

Members who were appointed and resigned during the year

Professor Stephen Evans* - London School of Hygiene & Tropical Medicine

Professor Ian Harvey* - School of Medicine, Health Policy and Practice
University of East Anglia

* Member appointed February 2006

Member appointed November 2006

Guest members who attended during the year

Feb 2006 - Dr Angela Cooper, MRC

July 2006 - Prof Robin Ferner, YCC Head West Midlands

Feb 2007 - Prof Nick Bateman YCC Head Scotland

Feb 2007 - Prof Kevin Park, University of Liverpool

Member biographies

Dr Brian Gennery (Chairman) has now retired and was most recently the Director of the Clinical Research Centre and prior to that Dean of the Postgraduate Medical School both at the University of Surrey. He has worked in pharmaceutical R & D for over 30 years, having worked for Boehringer Ingelheim, Eli Lilly and Chiroscience. He was a co-founder of Arakis and is immediate past President of the Faculty of Pharmaceutical Medicine. He teaches on the MSc course in Pharmaceutical Medicine at the University of Surrey. He is currently principle investigator on a clinical trial and consults for 4 small pharmaceutical companies. He has published 24 articles and book chapters on various aspects of Pharmaceutical Medicine.

Dr Jackie Cassell is Senior Lecturer in Clinical Epidemiology at the Brighton and Sussex Medical School, and a Consultant in Health Protection. 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.

Dr Corinne De Vries is Reader at the Postgraduate Medical School and Head of Pharmacoepidemiology, University of Surrey.

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 he is an Executive Editor of the *British Journal of Clinical Pharmacology*. He is 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).

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.

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.

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
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

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
Dr Jacqueline Cassell	None				
Dr 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
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

	PERSONAL INTERESTS		NON PERSONAL INTERESTS		
MEMBER	NAME OF COMPANY	NATURE OF INTEREST	NAME OF COMPANY	NATURE OF INTEREST	WHETHER CURRENT
Dr Martin Gulliford	None		None		
Prof Amrit Hungin	GlaxoSmithKline	Consultancy (for constipation therapies)	Proctor & Gamble	Research grant (inflammatory bowel disease)	Yes
	Red Door Consultancy	Consultancy (Rotavirus vaccination)	Wyeth	Research grant (reflux disease)	No
	Reckitt Benkiser	Consultancy (Gastro-oesophageal reflux disease)	Abbott	Research grant (H pylori infection)	No
	Proctor & Gamble	Research grant, travel and accommodation to professional meetings (Inflammatory Bowel Disease)	Novartis	Research grant (irritable bowel syndrome)	Yes
	Novartis	Consultancy (Irritable Bowel Syndrome)			
Prof Paul Little	Abbott Pharmaceuticals	Consultancy (two half day sessions on the complications of respiratory tract infections)	None		
Dr David Lovell	Pfizer	Shares, stock options, member of pension scheme	Emergent Bio Solutions	Member of safety monitoring committee	Yes
	AstraZeneca	Spouse owns shares			
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		
Ms Marcia Saunders	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.