

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

(ISAC)

3rd Annual Report

01 April 2008–31 March 2009

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Foreword from the Chairman of the Medicines and Healthcare products Regulatory Agency (MHRA)

I am once again delighted to launch the annual report for the Independent Scientific Advisory Committee for MHRA database research (ISAC).

The ISAC has now reviewed over 350 protocols, which illustrates the importance of MHRA data to the research community and the dedication shown by our Chairman and members to review a high volume of protocols on a weekly basis. There are ever-increasing calls for access to Government data and transparency of decision-making, and I am pleased that the ISAC review process is both transparent and efficient, as the statistics in this third annual report demonstrate. The average response time from the date of receipt of a General Practice Research Database (GPRD) protocol to providing initial feedback is 13 working days, which is our best figure yet.

We have again recruited additional members to the Committee: Dr Richard Stevens who brings expertise in statistics and Professor Barbara Pierscionek who is a new lay member. We greatly value the contribution of our lay members on MHRA committees and expert advisory groups. The MHRA's first Patient and Public Engagement Strategy published this year shows our commitment to patients and the public, and I am encouraged that the ISAC has already shown initiative in this area. This year the ISAC has considered the involvement of patients in Yellow Card and GPRD protocols, and produced a guidance document for Patient/User Group Involvement in GPRD studies.

Another patient involvement milestone for the ISAC has been reached with the publication of research using patients recruited from data submitted on Yellow Card reports. I would like to thank Professor Munir Pirmohamed from the University of Liverpool for his cooperation and patience in working with the MHRA to implement a process for contacting patients. This is a tremendous achievement as the 2004 *Independent Review of Access to the Yellow Card Scheme* which led to the establishment of ISAC envisaged Yellow Card data being available for exactly this type of research.

Finally, and on a personal note, I was very pleased to hear that past ISAC Chairman Dr Brian Gennery was awarded the MBE in the 2008 Queen's Birthday Honours for his service to MHRA committees. The MHRA can only supply data for research because of the expert review of the ISAC and I am very grateful to the current chairman Professor Adgey and the ISAC members for the devoted public service they provide.

Professor Sir Alasdair Breckenridge
MHRA Chairman
June 2009

Foreword from the Chairman of the ISAC

My first full year as the ISAC Chairman has been rewarding as it has revealed to me the high number of researchers both in the UK and internationally who value MHRA data. ISAC approval gives researchers access to a wealth of data and when deciding whether to grant approval ISAC is acutely aware of the attention to detail it takes to submit an approved protocol. This year, we have again reviewed a large number of protocols on a variety of topics.

Although the scientific expertise needed to review Yellow Card applications is similar to that for GPRD, we also have to ensure that this vital adverse drug reaction reporting scheme is not threatened by inappropriate use of its data. I am delighted that the benefits of using this database to contact patients are being exploited, however it is surprising that the limitations of the database, such as its inability to calculate incidence are still not widely known. Further guidance in the coming year will help researchers understand where Yellow Card data can add value to a study.

Although the ISAC does not perform ethical review we remain aware of the need for ethical consideration when reviewing protocols. I am grateful to members, in particular the lay members, for ensuring that researchers, the ISAC and the MHRA take ethical and patient interests into account when making decisions. Where necessary, ethical review by an NHS Research Ethics Committee (REC) complements ISAC review and I am grateful to all REC Chairmen who review applications for MHRA data. I am also pleased that our partnership with the Medical Research Council (MRC) for review of GPRD applications will continue into its fourth year.

I would like to thank ISAC members for their regular and prompt review of protocols as well as the MHRA Secretariat for their support throughout the year.

Professor Jennifer Adgey
ISAC Chairman
June 2009

1. Introducing the Independent Scientific Advisory Committee for Medicines and Healthcare products (MHRA) database research (ISAC)

1.1. Role and Terms of Reference of the ISAC

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 (01 April 2008–31 March 2009) there were fourteen professional ISAC members, chaired by Professor Jennifer Adgey, with expertise in statistics, epidemiology, general practice, paediatrics and clinical pharmacology. There were also two lay members. Full information on membership is included in Annex 1.

The ISAC reviews GPRD protocols using a two-team system. Protocols are circulated alternately to each team whose 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. Currently, Yellow Card applications are considered only at ISAC meetings.

1.3. Review of applications for Yellow Card data

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 the 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 requested data, 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 an 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 biases and confounding; and
- original case record verification is necessary.

2. Achievements of the third year

2.1. Outputs

- The ISAC met four times and reviewed a total of 113 GPRD protocols (electronically) and 4 Yellow Card applications for the first time (see Chapter 3).
- Of the total number of GPRD protocols reviewed, 34 sought data accessed under the GPRD-MRC scheme.
- The ISAC advised MHRA on a response to the NHS Connecting for Health *Consultation on Public, Patients, and other interested parties views on Additional Uses of Patient Data*.
- The ISAC produced a guidance document for Patient/User Group Involvement.
- Publication of the first research using a patient recruited through information submitted on a Yellow Card report.

2.2. Highlights of the third year's meetings

The four meetings held in the period covered by the third annual report were on Wednesday 30 April 2008, Friday 27 June 2008, Thursday 30 October 2008 and Tuesday 24 March 2009. Summary minutes of all these meetings have been published on the MHRA website.¹ The first part of the meeting on 24 March 2009 was an induction for the new members recruited that month. Meetings are structured with general discussion items followed by separate sections for Yellow Card and GPRD applications for data. Key issues discussed in meetings during the second year are outlined below.

2.2.1. Patient /User Group Involvement:

The Committee endorsed a guidance document produced by the lay members to assist researchers with the completion of the section on 'Patient/User Group Involvement'. The document has been published on the GPRD website www.gprd.com.

In March 2009 as part of the induction for new members the MHRA Patient and Public Engagement Manager spoke about initiatives MHRA are doing to increase patient and lay involvement in decision making. There are meetings for all MHRA committee lay members twice a year.

2.2.2. Research Governance

Committee members were concerned about the growing *misuse* of GPRD data by some users. This was clearly reflected in some protocols in which researchers appeared to have sufficiently explored or potentially answered their study questions before protocol submission to the ISAC. Although retrospective requests for protocol approval were not usually supported by the ISAC, in instances where this had been granted because of

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

exceptional circumstances, researchers would be required to declare this fact during the publication process.

2.2.3. Descriptive studies and hypothesis testing in GPRD

A number of protocols submitted for review were classified as 'descriptive studies' even though hypothesis testing was implied or explicitly stated. The Committee discussed whether there might be a need to conduct an audit of such studies to quantify the magnitude of the problem.

To resolve this issue, the Committee agreed that the ISAC application checklist should be updated to explicitly request the following information from applicants:

- whether hypothesis testing would be undertaken and the statistical methods applicable to the area of research;
- whether the study was of a descriptive nature and the statistical methods to be used; and
- the justification for not undertaking sample size calculations for the study. The current heading on data analysis should be expanded to include statistical analysis.

2.2.4. Protocol Deviations

The Committee agreed that decisions on what constituted substantial deviations from the protocol would be evaluated on a case-by-case basis. A substantial deviation would generally include testing a new hypothesis not previously stated in the protocol and significant changes in the design methodology and statistical analysis of the study. If a request for an amendment of protocol was deemed a substantial deviation from the initially approved protocol, the applicant would be required to submit a new protocol for full review.

2.2.5. GPRD external data linkage initiative

Following the successful linkage of GPRD core data to external data sources such as Hospital Episode Statistics (HES), Myocardial Ischaemia National Audit Project (MINAP) and Townsend Deprivation Score, the Committee has reviewed an increasing number of protocols requesting linkage to these data sources. The Committee has noted that applicants are often not aware that such data are currently only available for a subset of practices in the GPRD and how this may limit case finding, impact on sample size calculations and impact on the power of their proposed study.

2.2.6. Novel uses of the GPRD for research

The Committee reviewed a number of feasibility studies involving novel use of the GPRD for research. Such protocols were reviewed by the entire Committee rather than using the team approach in order to benefit from the wide expertise of all members.

2.2.7. Publication of results of a UK-wide study on drug-induced liver injury (DILI) that included Yellow Card data (ISAC application AYCD007)

A multicentre collaboration involving Newcastle, Liverpool, Nottingham and London conducted research to find genes predisposing to drug-induced liver injury (DILI). The research team was headed by Prof Ann Daly from Newcastle and the principal applicant for Yellow Card data was Prof Munir Pirmohamed from the University of Liverpool.

Drugs considered were anti-TB medications flucloxacillin and co-amoxiclav (Amoxicillin combined with clavulanic acid). UK-wide recruitment of cases was retrospective and prospective and inclusion criteria were:

- Clinical jaundice or Bilirubin > 40 mmol/l; or
- ALT >5x ULN; or
- ALP >2x ULN and Bilirubin > ULN.

The research team applied to use Yellow Card data in July 2005 which was granted approval following consideration by the Interim Committee on Yellow Card data in 2005 and by the ISAC in 2006. This was the first ISAC-approved study to involve contacting reporters through the Yellow Card Scheme to recruit patients. Ethical approval was granted by the Leeds (East) Research Ethics Committee. The study was funded by the UK Department of Health as part of the NHS White Paper on Genetics.

Twenty-five reporters were contacted, producing five positive responses and four negative responses. Four patients with drug-induced liver injury from co-amoxiclav and one with flucloxacillin were recruited into the study. Further recruitment is on-going via Yellow Cards. The data from patients with flucloxacillin-induced liver injury have provided novel insights into the mechanism and have the potential to substantially improve diagnosis of this serious disease. The findings were published in *Nature Genetics* in May 2009 (see 3.1.8). Further papers on co-amoxiclav induced liver injury are being prepared,

Although adverse drug reactions (ADRs) are multi-factorial in nature, the study shows that genetic factors are important in predisposing to ADRs. The Yellow Card database is a potentially valuable source for cases and should be used in conjunction with other methods of recruitment.

2.2.8. Release of Yellow Card reporter details

The Committee considered an information paper which was unusual as the researchers were not requesting any clinical details of individual Yellow Card reports submitted, but simply for the MHRA to put them in touch with reporters. The Committee noted that ethical approval had already been granted and that the scientific value of the application was real. This was an appropriate use of Yellow Card data. The Committee requested to see any other similar applications as the Committee has scientific overview of the release of Yellow Card data. This was especially important as release of reporter contact details in this way was still relatively new.

3. Applications considered by the ISAC from 1 April 2008–31 March 2009

3.1. Yellow Card : Consideration of applications

3.1.1. Total number of applications submitted to ISAC for the first time Apr 2008-Mar 2009

4

3.1.2. Number of applications submitted to ISAC for the first time Apr 2008-Mar 2009, by type of organisation to which the study's principal investigator was affiliated

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

3.1.3. Total number of applications approved by ISAC Apr 2008-Mar 2009

1

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

1

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

2

3.1.6. Information on applications approved by ISAC Apr 2008–Mar 2009

Ref	Principal Applicant	Title	Affiliation
AYCD017	Prof Nick Bateman	Assessment of the impact of a Scottish community pharmacy campaign on Patient Yellow Card reporting	University of Edinburgh

3.1.7. Information items considered by ISAC Apr 2008–Mar 2009

Ref	Principal Applicant	Title	Affiliation
AYCD019	Healthcare Commission	Use of Yellow Card reporting rates as a	Government

		performance indicator for the Healthcare Commission's Annual Health Check	
AYCD020	Dr Bridget Young	ADR reports for <16 year olds reported by either a parent/carer	University of Liverpool

3.1.8. Publications using Yellow Card data published since the last annual report

Daly AK et.al. HLA-B*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin. *Nat Genet* 2009; **41**: 816 – 19

<http://www.nature.com/ng/journal/v41/n7/abs/ng.379.html>

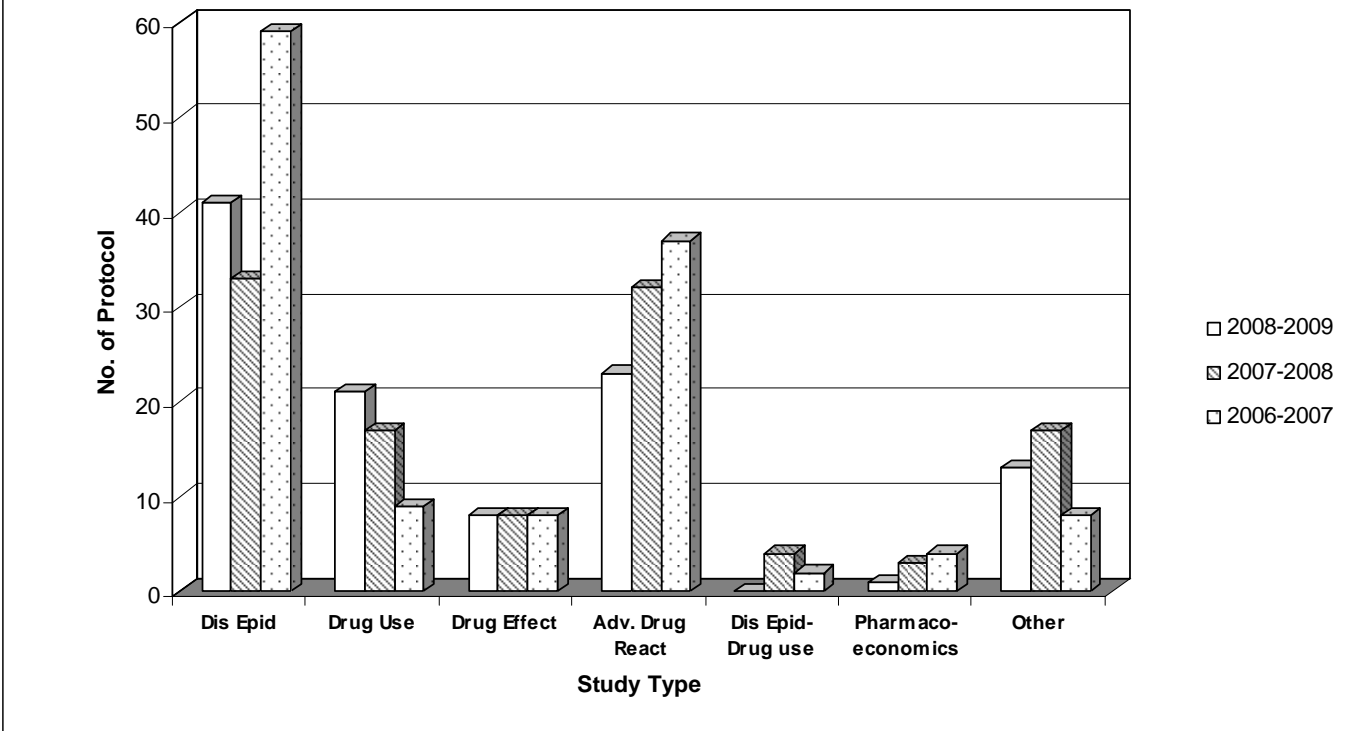
3.2. GPRD : Consideration of applications for data

3.2.1. During the period Apr 2008–Mar 2009, ISAC considered **113** 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. Fig 1 and Fig 2 show comparisons of protocols by study type and organisation for the period Apr 2006 –Mar 2009.

Table 1: Protocols submitted to ISAC for the first time Apr 2008-Mar 2009

Study type	Number of submissions	Percentage of total
Disease epidemiology only	47	41.6
Adverse drug reactions	17	15.0
Adverse drug reaction & Other	6	5.4
Drug use only	21	18.6
Drug effectiveness	4	3.5
Drug use & drug effectiveness	4	3.5
Pharmacoeconomics	1	0.9
Other	13	11.5
Total	113	100%

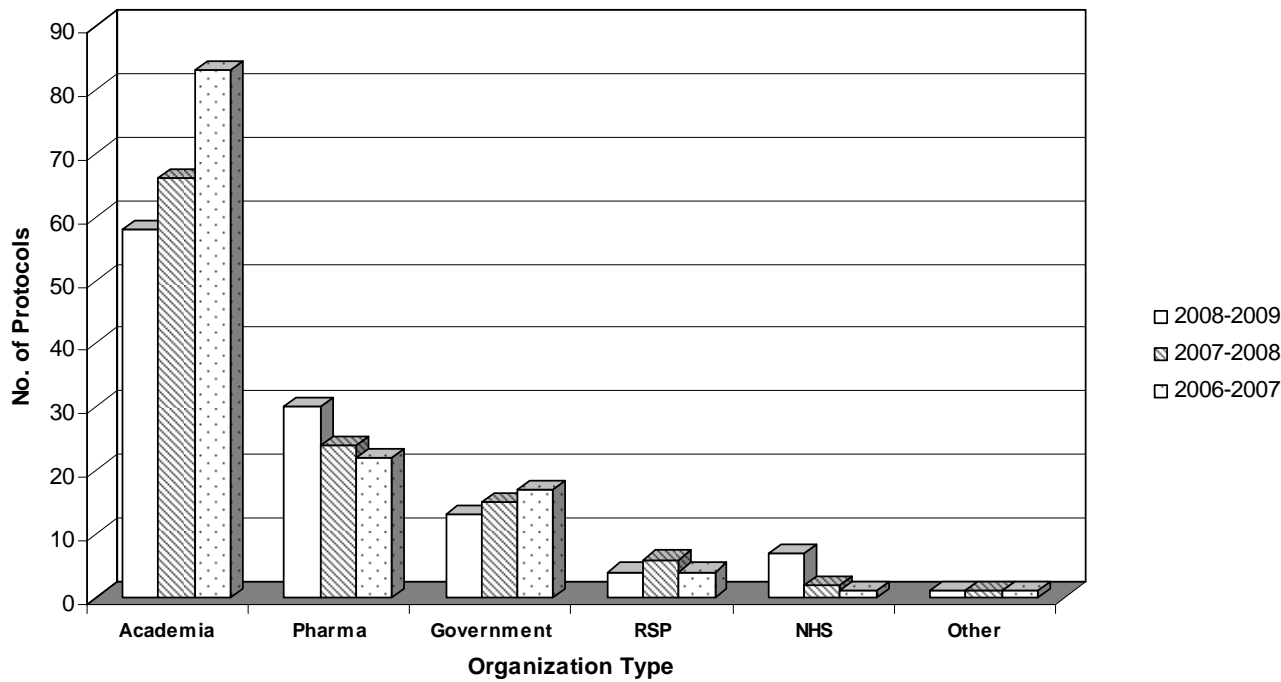
Fig 1. Protocol submitted to the ISAC for the first time during Apr 2006 - Mar 2009, by study type



3.2.2. Table 2: Protocols submitted to ISAC for the first time in Apr 2008–Mar 2009, by type of organisation to which the study’s principal investigator was affiliated

Organisation Type	Number of submissions	Percentage of total
Academia	53	46.9
Academia & Government	3	2.6
Academia & NHS	2	1.8
Pharmaceutical Industry	30	26.5
Research Services Provider	4	3.5
Government	13	11.6
NHS	7	6.2
Other	1	0.9
Total	113	100%

Fig 2. Protocols submitted to ISAC for the first time during Apr 2006 - Mar 2009, by organization type

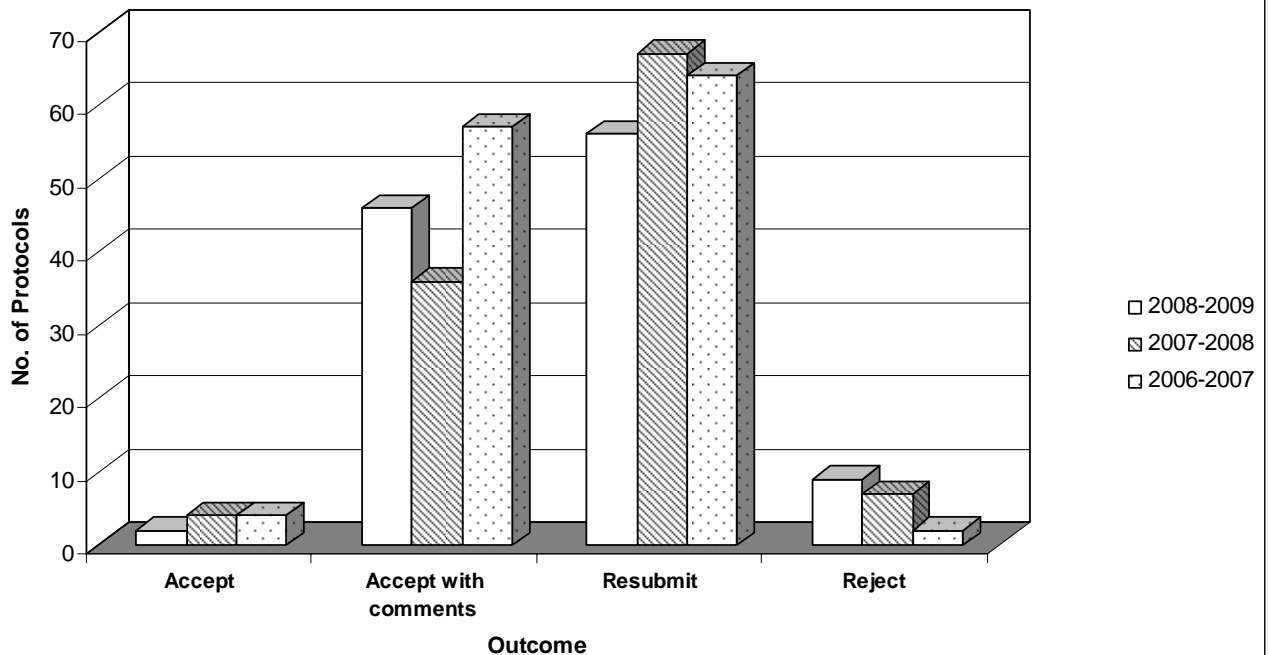


3.2.3. Table 3 gives a breakdown of the **113** first-time submissions from Apr 2008–Mar 2009 by the recommendation made by ISAC. Fig 3 shows a comparison of outcome following initial review for the period Apr 2006–Mar 2009.

Table 3: Protocols submitted to ISAC for the first time in Apr 2008–Mar 2009, by outcome of ISAC initial review

ISAC recommendation	Number of protocols	Percentage of total
Accepted	2	1.8
Accepted with comments	46	40.8
Revision requested	56	49.6
Rejected	9	8.0
Total	113	100%

Fig 3. Protocol submitted to ISAC for the first time during Apr 2006 - Mar 2009, by outcome on initial review



3.2.4. Table 4 shows 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 2008–Mar 2009 (excluding weekends)

Number of submissions	Median	Range (min-max)	Mean \pm SD
113	13	8-30	14 \pm 4

3.2.5. 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 **34** submissions considered during the period Apr 08 – Mar 2009. Tables 5 and 6 below show a breakdown of these protocols by study type and reviewing outcomes.

3.2.6. Table 5: MRC Protocols submitted to ISAC for the first time in Apr 2008-Mar 2009, by study type

Study type	Number of submissions	Percentage of total
Disease epidemiology only	16	47.1
Adverse drug reactions	5	14.7
Drug use only	3	8.8
ADR & drug use	1	3.0
Drug effectiveness	3	8.8
Pharmacoeconomics	-	-
Other	6	17.6
Total	34	100%

3.2.7. Table 6: MRC Protocols submitted to ISAC for the first time in Apr 2008-Mar 2009, by outcome of ISAC initial review

ISAC recommendation	Number of protocols	Percentage of total
Accepted	-	-
Accepted with comments	14	41.2
Revision requested	14	41.2
Rejected	6	17.6
Total	34	100%

3.2.8. 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>

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) who provide secretariat for Yellow Card data 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. Members access papers through the MHRA Portal which is more secure than using email, or hard copy by Royal Mail Special Delivery.

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 during the reporting period were:

	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 for 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 in Annex 1 and duties of members are in 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 in Annex 5.

4.7. Appraisals

It is a condition of appointment that members engage in an annual appraisal process with the Chairman.

4.8. Freedom of Information and Publication scheme

Summary minutes of meetings are published on the MHRA website once full minutes have been agreed.² Unless a FOIA exemption applies, general sections of the minutes are published in full. Information on applications is only published in summary minutes when an application has been approved, including the title/subject of the study and ISAC's conclusion. 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

2

<http://www.mhra.gov.uk/Committees/IndependentScientificAdvisoryCommitteeforMHRAdatabaseresearch/Minutes/index.htm>

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, however the first report covered 1 February 2006–31 March 2007 because of the date the Committee was established.

4.9. 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 in Annex 6.

5. Background to work of the MHRA

The 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 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 and included a 24-week public consultation period.³

3

http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON024108

In January 2005, the Government responded to recommendations of the Review about widening access to Yellow Card data, together with other recommendations on enhancing the operation of the Yellow Card Scheme.

The 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 four 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 GPRD

The 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 over 4.29 million active patients (10 million patients ever of which 8.16 million are research usable) from over 500 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 research⁴.

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 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.

⁴ Data subject: 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.

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 GPRD. Between 1994–1999 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 (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 was 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 multi-disciplinary team within the MHRA responsible for all aspects of the operation and management of the GPRD. It comprises 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 nine 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 maximize 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 and 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 505 general practices across the United Kingdom. As of August 2009, the number of currently registered ('active') individuals in the GPRD is 4.29 million, representing 36.41 million person years of follow-up. In total, there are about 8.2 million research usable patients 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 and post code). 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 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.

The work of the GPRD is covered by MREC approval granted by the Trent Multi- Research Ethics Committee.

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, copy the data, 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 IDCs extracted at the practice and from any new patients who have registered since the previous collection. IDCs are requested on a 6–8 week cycle, subject to the practice carrying out their collections in a timely manner, the collection being of acceptable quality and the collection file passing the technical integrity checks.

The MHRA has a contract with In Practice Systems that ensures that GPRD data collection continues 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 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 patient data fields 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, but this is only effective if it 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 as it provides additional information about medical conditions. This might include information that might otherwise not be recorded in the main medical record because there is no specific Read code⁵ (e.g. for rhabdomyolysis, 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 collected from practices is 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

⁵ 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.

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)⁶. 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.

This aspect of GPRD work is covered by Trent MREC approval.

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, pharmacoconomics and health service planning) are becoming more common. Since 1988, over 650 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 the MMR vaccine and autism, and selective serotonin reuptake inhibitors (SSRIs) and self-harm/suicide.

5.2.8. Access to GPRD data under the MRC licence

Collaboration between the GPRD Group and the MRC was implemented in December 2005. The MRC licence funds access to specific cuts of GPRD data for UK academic groups over a five-year period. The licence will fund up to 50 academically-led proposals per year. Any UK-based researcher who can demonstrate that they will direct the proposed research and be actively engaged in carrying it through is eligible to apply for access to GPRD data under this initiative. Applicants must be based at a higher education institution approved by the Council. Principal investigators based overseas, retired researchers as the sole or principal applicants and students are not eligible to apply.

Full details of the conditions of access to the GPRD under the MRC licence are listed on the GPRD website (www.gprd.com). In particular, there is a restriction on use to include only academic research projects that are not directly supported by other sources. These academic projects must have no

⁶ 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 ISAC

commercial funding nor be linked with any other commercial funding that the institution or department may have. Additionally, GPRD datasets cannot be used as teaching tools.

5.2.9. Linkage of GPRD to external data sources

In 2007, GPRD began an initiative to link GPRD data to a number of external data sources to enhance the research capacity of the database. External data sources that will be linked include:

- HES
- The Cancer Registry Data
- ONS Death Data
- Cardiovascular Registry (CCAD)
- Indices of Deprivation (Townsend scores and Index of Multiple Deprivation)

Data linkage is through a trusted third party and GPRD contributing practices are required to consent to participate in the programme.

Annex 1 – ISAC Membership and member biographies

Professor Jennifer Adgey (Chairman) CBE MD FRCP FACC FESC DSc

(Hons)⁺: Honorary Professor of Cardiology Queens University & Honorary consultant in cardiology, Royal Victoria Hospital, Belfast

Professor Jacqueline Cassell FFPH FRCP MD MSc DipGUM DFFP[#]: Professor in Primary Care Epidemiology and 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 MD PhD FRCP FRACP[#]: Head, School of Graduate-Entry Medicine & Health, and Professor of Vascular Medicine, University of Nottingham

Professor Martin Gulliford MA FRCP FFPH[#]: Professor in Public Health at King's College London

Professor Amrit (Pali) Hungin OBE MD FRCGP FRCP FRSA^{*}: 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 T Kadam MRCGP MPhil MSc PhD⁺: GP Epidemiologist, Research Institute for Primary Care and Health Sciences

Professor Paul Little MBBS MRCP MSc MD FRCGP^{*}: GP and Professor of Primary Care Research at the Aldermoor Health Centre, Southampton University.

Dr David Lovell PhD BSc (Hons) FSS FIBiol CStat CBiol[#]: Reader in Medical Statistics, University of Surrey

Professor Richard Martin BMedSci BM BS MRCGP FFPH MSc PhD[#]: Professor in Clinical Epidemiology, Department of Social Medicine, University of Bristol

Ms Barbara Meredith[∨]: Lay member

Dr Sarah Meredith MBBS MSc MRCGP FFPH (Deputy Chair)^{*}: MRC Clinical Trials Unit

Professor Simon Mitchell MD MRCP FRCPCH DCH DRCOG⁺: Consultant Neonatal Paediatrician St Mary's Hospital Manchester, Honorary Professor, School of Health Care Professions, University of Salford

Professor Barbara Pierscionek PhD MBA LLM[^]: - Lay member and Professor of Vision Science, University of Ulster

⁺ Member appointed November 2007

[^] Member appointed February 2009

^{*} Member reappointed February 2009

[#] Member appointed November 2006

[∨] Term of office expired February 2009

Ms Marcia Saunders BA MA MSc[#]: Lay member

Dr Richard Stevens BA MSc PhD[^]: Senior Statistician, Division of Public Health and Primary Care, University of Oxford

Dr Ruben Thanacoody MD FRCP (Edin)⁺: Consultant Physician, Royal Victoria Infirmary, Newcastle Upon Tyne Hospitals NHS Trust, Consultant Clinical Toxicologist, NPIS (Newcastle) and Yellow Card Centre (Northern and Yorkshire), Regional Drugs and Therapeutics Centre and Honorary Senior Lecturer in Clinical Pharmacology, University of Newcastle-upon-Tyne

ISAC Member biographies

Professor Jennifer Adgey (Chairman) is 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 is Professor of Primary Care Epidemiology and Honorary Consultant in Health Protection and in Genitourinary Medicine at 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. 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 individuals 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 and rheumatoid arthritis.

Professor Richard Donnelly is Head of the School of Graduate-Entry Medicine & Health, and Professor of Vascular Medicine at 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*, 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 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 fields 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 self help, the management of common illnesses, and health promotion. He has been an advisor to the National Institute for Health and Clinical Excellence on several guidelines and technology appraisals, serves on the MRC/NIHR Efficacy and Mechanisms Evaluation (EME) 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.

Professor Richard Martin is Professor 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 NICE. 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 MRC 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.

Professor 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 the Health Technologies Appraisals Committee at NICE.

Professor Barbara Pierscionek was appointed to a Chair in the Department of Biomedical Sciences at the University of Ulster in 2004 where she is Research Leader of the Vision Science research group and where she is engaged in research on optics, rheology, proteomics and molecular biology of the anterior eye as well as healthcare ethics and medical law. Prior to this she worked as a Senior Research Fellow in Biomedical Sciences at The University of Bradford which she joined in 1997. Her previous experience was in Melbourne, Australia where she was supported by the Australian Medical Research Council to develop research on the structure/function relationships in the anterior eye and the changes that occur with ageing.

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 a member of the Board of Governors, De Montfort University, Leicester.

Dr Richard Stevens joined the Department of Primary Health Care in Oxford as a senior medical statistician in 2008. His previous experience includes 8 years at the Oxford Centre for Diabetes, Endocrinology and Metabolism, where he worked with the UK Prospective Diabetes Study group on the epidemiology and computer modelling of the cardiovascular complications of type 2 diabetes, and 3 years with the Cancer Research UK Epidemiology Unit, where he studied pancreatic cancer in the Million Women Study cohort. At the Department of Primary Health Care he contributes to the monitoring and diagnosis research program and the Centre for Evidence-Based Medicine teaching program.

Dr Ruben Thanacoody is Consultant Physician in the Royal Victoria Infirmary, Newcastle Upon Tyne Hospitals NHS Trust. He has a longstanding interest in pharmacovigilance and is involved in Yellow Card Centre (Northern and Yorkshire). His research interests include drug-induced QT prolongation and adverse reactions to acetylcysteine.

Annex 2 Duties of ISAC 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 the following 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 (now CHM)
- 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
DILI	Drug-induced liver injury
DPA	Data Protection Act 1998
FOIA	Freedom of Information Act 2000
GP	General Practice (or General Practitioner)
GPRD	General Practice Research Database
HES	Hospital Episode Statistics
ISAC	Independent Scientific Advisory Committee for MHRA database research
ISPE	International Society for Pharmacoepidemiology
IT	Information Technology
MCA	Medicines Control Agency (became MHRA in 2003)
MINAP	Myocardial Ischaemia National Audit Project
MMR	Measles Mumps and Rubella
MREC	Multi-centre NHS Research Ethic Committee
MRC	Medical Research Council
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
ONS	Office of National Statistics
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

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
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

	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 Johnson & Johnson Eli Lilly	Speaker fees Consultancy administered through University of Nottingham Co-investigator & consultancy	None		
Dr Martin Gulliford	None		None		
Prof Amrit Hungin	Reckitt Benckiser Italian Medicines Agency	Consultancy & education provision Ext Advisor	Reckitt Benckiser Novartis	Research grant Research grant	Yes No
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		

	PERSONAL INTERESTS		NON PERSONAL INTERESTS		
MEMBER	NAME OF COMPANY	NATURE OF INTEREST	NAME OF COMPANY	NATURE OF INTEREST	WHETHER CURRENT
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	None		None		
Prof Barbara Pierscionek	None		None		
Ms Marcia Saunders	None		None		
Dr Richard Stevens	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.