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

(ISAC)

Annual Report

Jan 2013- Dec 2013

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Foreword from the Chairman of the MHRA:

I am delighted to present the Independent Scientific Advisory Committee (ISAC) Annual Report (Jan 2013 to Dec 2013) for MHRA database research.

The work of the ISAC continues to grow, this year being no exception, with high quality advice provided by the Committee on over 223 protocols, which represents a 34% increase over 2012. The ISAC ensures that MHRA data are used to support public health research, while protecting the interests of patients and the public. The Committee remains transparent in the fulfilment of its remit and aims continuously to develop its efficiency and performance.

The Yellow Card data are vital in supporting drug safety research and monitoring, and work is underway to facilitate electronic Yellow Card reporting through integration into clinical IT systems used by healthcare professionals. This will improve the recording of adverse drug events increasing the quantity and quality of data, and will lead to greater use of Yellow Card data for drug safety research.

The Clinical Practice Research Datalink (CPRD), jointly funded by the NHS National Institute for Health Research (NIHR) and the MHRA, continued and intensified its research activities during 2013. In addition to increases in protocols, publications and national and international collaborations on observational research, CPRD presented its plan for the Clinical Trials suite of tools to facilitate interventional research.

On behalf of the CPRD and the Yellow Card scheme I wish to express my gratitude to the Chairman, Professor Patrick Waller, and all of the ISAC members for the expertise that they bring to the Committee and for the invaluable public service that they provide.

Professor Sir Gordon Duff
MHRA Chairman

Foreword from the Chair of the ISAC

Foreword from the Chair of ISAC

The Committee has had a busy year with the number of new CPRD protocol submissions increasing by 34% from 2012. To help with the expected increase in workload we welcomed five new members to the Committee at the beginning of the year - Krishnan Bhaskaran, Benjamin Cairns, Christopher Edwards, Iskandar Idris and Sally Malin. I should like to thank them and all the members of Committee for their contributions to the meetings and protocol reviews. I am also grateful to the Deputy Chair, Professor Jacqueline Cassell, for covering urgent business during periods when I have been unavailable.

Looking forward, a further increase in our workload on the CPRD side is projected, not only in volume but also a result of complexity and opportunities arising from additional linkages.

I should like to recognise here the excellent support we have received from the ISAC Secretariat throughout the year. On the CPRD side, Kendal Chidwick and Jessie Oyinlola have worked very hard to cope with the very large volumes of work now being received. In relation to the Yellow Card side, support from Sharon Jethwa has also been much appreciated.

Professor Patrick Waller
Chair ISAC

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 Clinical Practice Research Datalink (CPRD) 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 Clinical Practice Research Datalink;
- 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 relating to other ethical or confidentiality issues. This must be considered alongside input from other Committees such as Ethics and National Information Governance Boards (NIGB).

1.2. Membership and operation of the ISAC

During the year there were thirteen professional ISAC members and two lay members. Specific expertise was available in the fields of statistics, epidemiology, public health, general practice, paediatrics, clinical pharmacology and medical physics. Full information on membership is included at Annex 1. Research protocol submissions are reviewed on a continuous basis throughout the year and rarely require discussion 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 CPRD protocols

When reviewing CPRD protocols the Committee considers whether:

- The CPRD is a suitable database in which to conduct the research;
- There is a well defined hypothesis or clear question to be addressed where appropriate;
- There is compliance with the requirement to ensure protection of practice and patient confidentiality;
- The methodology is considered appropriate, including consideration of possible bias and confounding; and
- There are no remaining scientific concerns with the medical, statistical, epidemiological or methodological aspects of the study.

2. How the ISAC is organised

2.1. Secretariat

There are two ISAC secretaries, one for CPRD matters and one for Yellow Card matters. This is to ensure that discussions and outcomes arising from the review of CPRD protocols do not influence decision making by the regulatory staff of Vigilance and Risk Management of Medicines Division (VRMM) division who provide secretariat for Yellow Card applications.

CPRD queries can be sent to isac@cprd.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/Committees/IndependentScientificAdvisoryCommitteeforMHRAdatabaseresearch/index.htm

2.2. Meetings

ISAC meetings are usually held four times per year at the MHRA offices located 151 Buckingham Palace Road, Victoria, London, SW1W 9SZ.
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.

2.3. Electronic working between meetings

Due to the tight deadlines for review and the volume received, review of the majority of CPRD and Yellow Card protocols is performed electronically between meetings, with responses coordinated by the Chairman.

2.4. 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 associated to disabled members;
- Other reasonable expenses incurred e.g. locum costs, child care, overnight stay subject to agreed Agency limits.

2.5. Appointment of members

The Chair and members of the ISAC are appointed by the Department of Health (DH) Appointments Commission (formerly NHS Appointments Commission) for periods of up to three years which may be renewed up to a maximum of 10 years. Full information on current membership is at Annex 1 and duties of members are at Annex 2.

2.6. 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 Chair for cases where the Chair has a direct conflict of interest or is unavailable. A full declaration of members' interests is at Annex 5.

2.7. 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 currently 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 CPRD 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 are made available on the MHRA website.

2.8. 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 described at Annex 6.

3. Achievements of the Committee

3.1. Outputs

The Committee met 4 times on 23 January, 17 April, 10 July and 22 October 2013. Summary minutes of all these meetings have been published on the MHRA's website. During the year it reviewed and provided feedback on a total of 1 Yellow Card application (see Chapter 4) and 223 CPRD protocols (see Chapter 5) for the first time.

3.2. Operation of the risk review systems

3.2.1. CPRD protocols

The purpose of the Committee's review of CPRD protocols is to ensure that investigators using the databases for research have feasible plans which do not raise governance concerns and reach an acceptable scientific standard. In this context we aim to provide timely, high quality peer review of protocols whilst recognising that the quality of the research ultimately remains the responsibility of the applicants.

A risk review system for CPRD protocols has been operation since January 2012. Initial review of every protocol is undertaken independently by Chair and CPRD secretary using a structured form in order to assess systematically potential scientific and governance issues. Each protocol is rated as low, medium or high risk based on this assessment which takes into account the nature of the study and the potential implications for public health. Basic epidemiology or drug utilisation studies which do not raise significant concerns are rated low risk whereas more complex drug safety studies are rated high risk, even when they appear to be well-designed.

The underlying purpose of the risk review system is to enable the review capacity of the Committee to be focused on those protocols which are most likely to benefit from detailed peer review. Straightforward low risk studies are determined quickly through Chairman's action, although all studies continue to receive feedback based on comments made in the risk review process. Those protocols judged medium or high risk are reviewed further by members of the Committee.

The system whereby the Chair identifies two (or, exceptionally, three) members to review each medium or high risk protocol within 2 weeks has continued to function well

with 136 reviews commissioned and received i.e. there was a 100% response rate from members during this year.

The data given in more detail in section 5 below shows that the time taken to reach an initial decision has decreased further from an average of 11 days in 2012 to 8 in 2013. The proportion of protocols requiring resubmission decreased from 65% to 55%. It should be noted that resubmissions are given high priority and, during the year, almost all were determined within a few days of their receipt. Two further expected changes were a 37% increase in the proportion of protocols requesting use of linked data and a 125% increase in the number of amendments submitted over 2012. The latter followed the introduction of new guidance on amendments in July 2012.

During 2013 the risk review process was amended to give greater consideration to issues of confidentiality. After discussions with the Confidentiality Advisory Group of the Health Research Authority, a three level risk rating system for confidentiality (low/medium/high) has been applied to each protocol in addition to the overall risk rating system. The confidentiality rating is based on the numbers of datasets to be linked and other factors which could potentially increase the risk of deductive disclosure. Medium risk protocols are required to contain evidence of risk mitigation and high risk protocols are being referred to the Confidentiality Advisory Group before approval is granted. The application form was revised accordingly and use of the new version of form became mandatory from 15 July.

3.2.2. Yellow card protocols

Since June 2012, Yellow card protocols have been initially reviewed using a risk review process similar to that described above for CPRD protocols. However, volumes are low for Yellow Card data and to date, only two protocols have been reviewed in this way.

3.3. Revision of existing guidance

3.3.1. CPRD protocols

The Committee began a further review of its guidance to applicants and the revised guidance will be finalised and published on the CPRD website, with changes highlighted early in 2014. In order to improve the information available on which to

assess the expertise of applicants, the Committee asked the Agency to set up a system for requesting a brief curriculum vitae from all applicants. A statement of all potential competing interests will also be requested from applicants once the revised application form is introduced during 2014.

3.3.2. Yellow card protocols

The Yellow Card application form was recently updated, with the guidance notes now being separated from the application form making it easier for applicants to complete. Applicants are now required to submit a structured protocol detailing the aims and methods of the study they wish to conduct.

3.4. Audit of ISAC approved protocols through comparison with publication

During the year the ISAC discussed and agreed protocols for two studies which will be taken forward in 2014. The first will be undertaken by CPRD based on all protocols approved during 2008 and has the following objectives:

1. To establish the proportion of ISAC approved protocols which result in a publication in a journal.
2. For those protocols which result in publication, to establish the lag time from ISAC approval to publication.

The second will be undertaken by members of the Committee and its objectives are:

1. To link all publications in 2013 with their ISAC approved protocol, identifying any publications for which there was no ISAC approved protocol.
2. To compare the objectives, design and analyses between protocol and publication to identify and assess the extent of major deviations from ISAC approved protocols.
3. To measure the time elapsed between approval and publication.

3.5. System for setting and reviewing the objectives of members

At its April meeting the Committee agreed a new procedure for setting and reviewing the objectives of its members. Reviews are undertaken triennially and linked to the reappointment cycle. Reappointment is conditional on the objectives being met. The procedure was successfully used later in the year to assess the performance of the three members who were reappointed at the end of 2013.

4. Yellow Card Applications considered by the ISAC

4.1. Yellow Card Applications (Jan 2013 – Dec 2013)

4.1.1. During Jan 2013 – Dec 2013 one application was submitted to ISAC, this was submitted from an academic institute. ISAC requested further information for this application.

5. CPRD Research Applications considered by the ISAC

5.1. CPRD Applications (Jan 2013- Dec 2013)

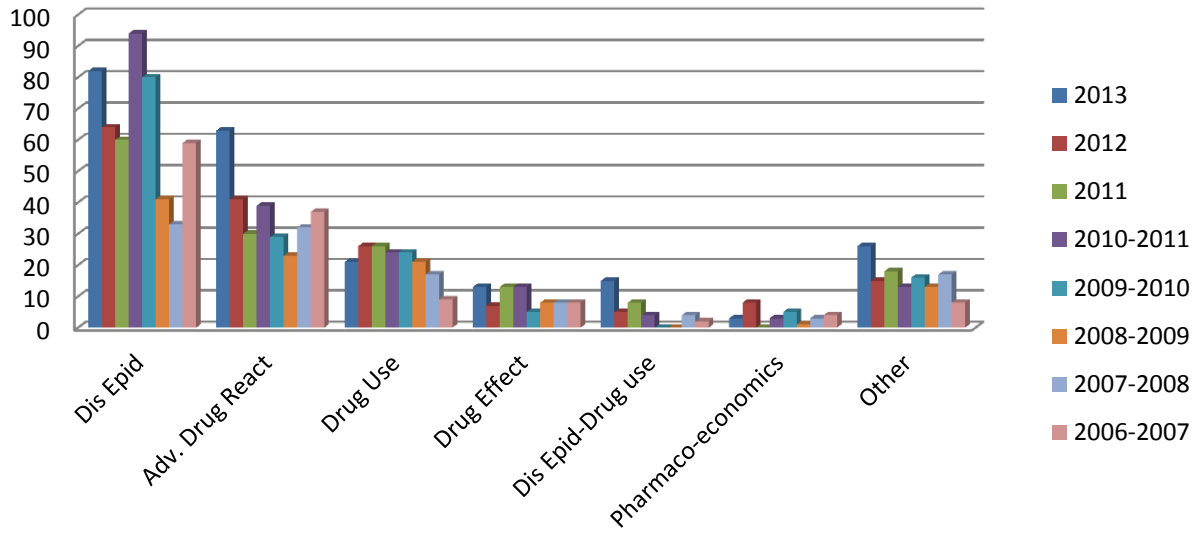
5.1.1. During the period Jan 2013-Dec 2013, ISAC considered 223 new CPRD protocols, a 34% increase over the same period in 2012. Tables 1 and 2 show a breakdown of these protocols by study type and organisation to which the principal investigator was affiliated, respectively. Figures 1 and 2 show a comparison of the breakdown year on year. Please note that until 2011 the annual report covered the financial year, and for 2011 and 2012 the reported figures relate to the calendar year.

5.1.2. **Table 1: Protocols submitted to ISAC for the first time during Jan 2013-Dec 2013, by study type**

Study type	Number of submissions	Percentage of total
Adverse Drug Reactions	47	21.1
Adverse Drug Reactions / Drug Effectiveness	6	2.7
Disease Epidemiology	74	33.2
Disease Epidemiology & Adverse Drug Reaction	10	4.5
Disease Epidemiology & Drug Use	15	6.7
Disease Epidemiology & Pharmacoec	8	3.6
Drug Effectiveness	13	5.8
Drug Use	21	9.4
Other*	26	11.7
Pharmacoeconomics	3	1.3
Total	223	100.0

**Study types under 'other' included health services research, methodological research and clinical trial feasibilities.*

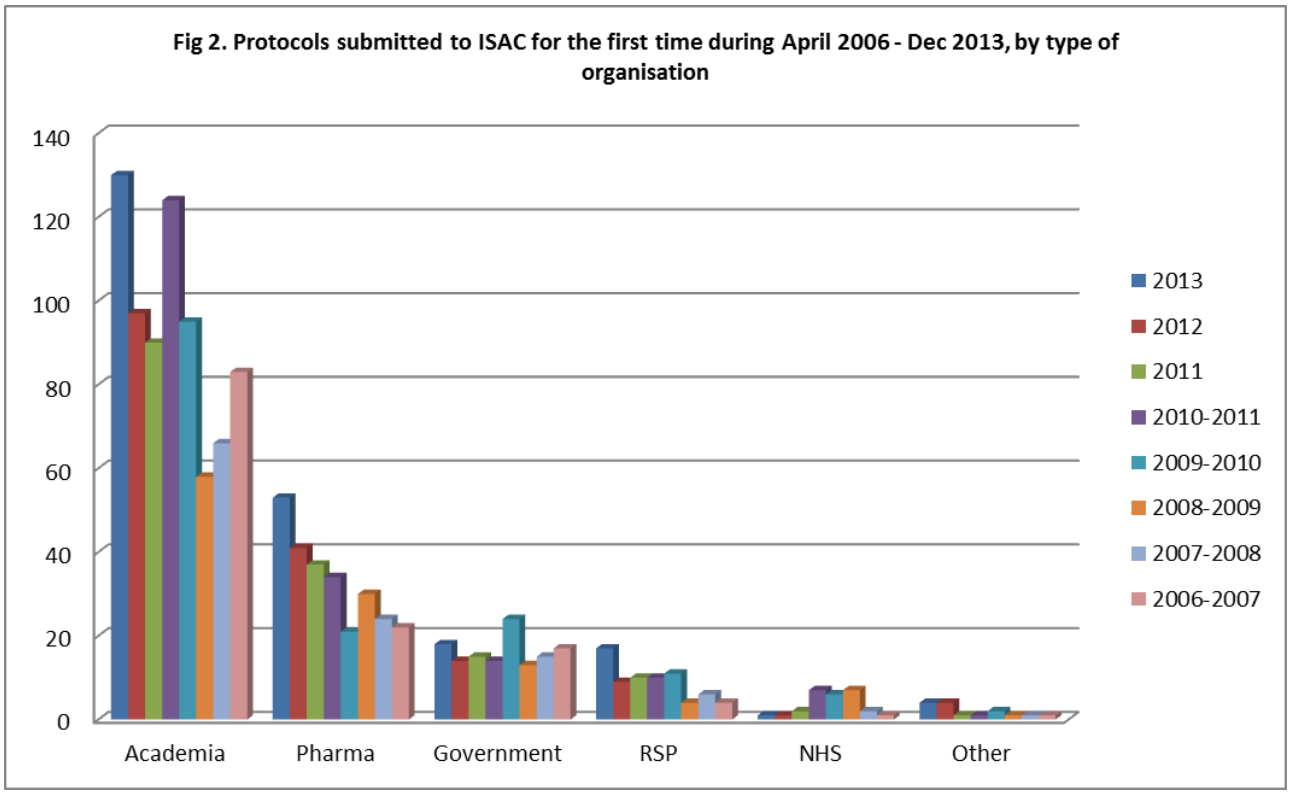
Fig 1. Protocols submitted to ISAC for the first time during April 2006 - Dec 2013, by study type



5.1.3. Table 2: Protocols submitted to ISAC for the first time in Jan 2012 – Dec 2012, by type of organisation to which the study's principal investigator was affiliated

Organisation Type	Number of submissions	Percentage of total
Academia*	130	58.3
Academia & NHS	1	0.4
Pharmaceutical Industry	53	23.8
Research Services Provider	17	7.6
Government	18	8.1
Other	4	1.8
Total	**223**	**100.0**

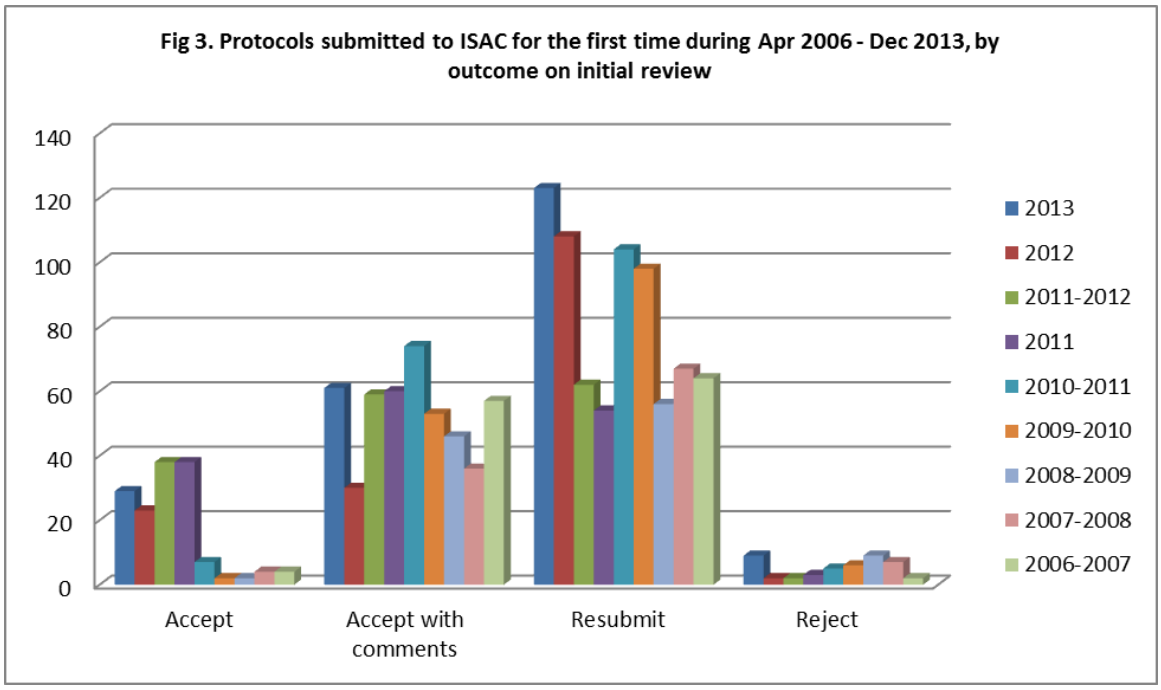
*note some of these studies were funded by a non-academic sponsor; 29 by Government (NIHR grant, MRC grant or other), 11 by the pharmaceutical industry, and 7 by a Charity.



5.1.4. **Table 3** gives a breakdown of the 223 first-time submissions from Jan 2013-Dec 2013, by the recommendation made by ISAC and Figure 3 shows this year on year.

Table 3: Protocols submitted to ISAC for the first time in Jan – Dec 2013, by outcome of ISAC initial review

ISAC recommendation	Number of protocols	Percentage of total
Accepted	29	13.0
Accepted with comments	61	27.4
Revision requested	123	55.2
Rejected	9	4.0
On hold	1	0.4
Total	**223**	**100.0**



5.1.5. **Table 4** details the time taken for CPRD submissions to be processed by ISAC. There was continued improvement in the time taken to provide the ISAC feedback after the initial application over the previous year (an average of 8 days in 2013, compared to 11 days in 2012 and 30 days in 2011).

Table 4: Elapsed time (in days) between receipt of protocols and questionnaires by ISAC secretariat and dispatch of initial ISAC evaluation to applicant Jan - Dec 2013 (excluding weekends)

Number of submissions	Median	Range (min-max)	Mean
223	6	1 – 33	8

5.1.6. **Table 5** shows the total number of amendments submitted to ISAC in 2012 and 2013, and by outcome. The number of amendments submitted to ISAC in 2013 versus 2012 more than doubled.

Table 5: Protocol amendments submitted to ISAC during 2012 and 2013, by outcome of ISAC review

ISAC recommendation	2012	2013
Accepted	*20*	*47*
Revision requested	*2*	*5*
Rejected	*2*	*2*
Total Amendments	**24**	**54**

5.1.7. Access to Linked Data Sources

A total of **123** studies sought access to linked CPRD data. This is an increase of **37%** over the number of studies seeking access to linked data in 2012. A breakdown of requests for linked data sources is provided in Table 5. Please note that access to one or more linked data source was requested for some studies.

Table 5: Protocols seeking access to linked CPRD data in Jan 2013 - Dec 2013

Linked Data Source	Requests
Any Linked data source	**123**
Hospital Episode Statistic (HES)	93
Townsend /IMD Score	66
ONS Mortality Data	60
Cancer Registry Data	22
MINAP Registry Data	7
Hospital Treatment Insights (HTI)	2
Other (bespoke)	2

5.2. CPRD Publications

The findings of many studies approved by ISAC were published as research papers in international journals. A comprehensive list of publications based on data from the CPRD is published on the CPRD website (www.cprd.com/bibliography).

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 CPRD GOLD 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 700,000 UK reports have been received. Approximately 26,000 UK reports of suspected ADRs per year have been received in recent years, with an increase to approximately 30,000 in 2013 due to a number of initiatives.

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.

6.2. Background on the Clinical Practice Research Datalink

The main primary care database held by the Clinical Practice Research Datalink (CPRD) is called GOLD (formerly GPRD). CPRD GOLD contains the anonymised longitudinal health records collected from primary care (general practices) across the United Kingdom. The database currently contains data for over 13.2M acceptable (research quality) patients, of which 5.69M are active (still registered with a contributing GP practice) from 680 UK practices. The database is managed by the CPRD Group at the MHRA on behalf of the Secretary of State for Health.

The CPRD GOLD database 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 CPRD GOLD, research involving these data is most often observational data subject research[1]. Since its inception, in excess of 1,100 research papers based on CPRD 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 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.

[1] 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.

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.

In March 2011, the Government's Plan for Growth was published setting out the path for implementation of a viable and affordable research data service based on the work of the Department of Health's NIHR Research Capability Programme (RCP). In April 2012 the Clinical Practice Research Datalink was launched as the new English NHS observational data and interventional research service, jointly funded by the NHS National Institute for Health Research (NIHR) and the MHRA. The CPRD combines the expertise of the GPRD and the RCP which piloted the potential for a larger, wider service over the previous four years.

6.2.2. The CPRD Group

The CPRD is a Centre within the MHRA responsible for all aspects of the operation and management of the CPRD. It comprises a multi-disciplinary team of around 45 staff, led by Dr John Parkinson, who has extensive experience managing anonymised patient databases (10 years MEMO, Tayside, University of Dundee, prior to GPRD/CPRD).

In 2013 the CPRD Research Team comprised 9 staff, including epidemiologists and statisticians, and was headed by Dr Tjeerd van Staa who has extensive experience in pharmacovigilance and epidemiology, and has published widely on research using CPRD data.

The CPRD Group aims to maximize the use of the CPRD GOLD database to support public health research, both in the UK and internationally, based upon the research utility of this key dataset and linked datasets 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

As of October 2013, the CPRD collected data from 680 general practices across the United Kingdom. The number of registered (‘active’) individuals in the CPRD was 5.69 million. In total, there are about 13.2 million research usable patients represented in the database.

The CPRD 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 pseudonymised data is adopted by CPRD and technically does not require consent. However, CPRD works with contributing practices to ensure patients are aware of such use of their data and of their right to dissent from the use of their pseudonymised data 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 CPRD.

The core work of the CPRD is covered by the favourable opinion granted on the 2nd August 2012 by a meeting of the "NRES Committee East Midlands - Derby" of the National Research Ethics Service established by the Health Research Authority. The REC reference number is 05/MRE04/87. N.B. the REC reference is the same as that for GPRD, because it was established as a substantial amendment. The work of CPRD is also covered by Section 251, CAG approval.

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 CPRD GOLD 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 compressed encrypted extract on USB and contains the required details for every collection (Collection type, audit sequence number for collection start, etc.) Practice staff initiates the collection, check the data if they wish, back it up to media, and return it to the CPRD 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 daily or monthly basis, 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 majority of IDCs are now done automatically; these Auto Collections are compressed, encrypted and automatically transferred directly from the Practice to a Data server via Vision Data Transfer (VDT).

The MHRA has a contract with In Practice Systems to ensure that CPRD data collections remain uninterrupted in the event of upgrades to the Vision software.

6.2.5. Pseudonymisation

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 CPRD Group or by researchers using CPRD 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 CPRD 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 code[2] (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 CPRD GOLD.

Although the Recording Guidelines for Vision Users (issued by the CPRD 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

[2] 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.

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 CPRD Data Warehouse, following an exercise to remove patient identifiable information from around 100,000 distinct free text phrases (accounting for around 95% of all entries in the dosage instructions field).

For free text other than the 'dosage instructions', the CPRD 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 CPRD Operations Team under the terms of a Standard Operating Procedure previously approved by the Scientific and Ethical Advisory Group (SEAG)[3]. The CPRD Research Team access free text in the same way as any other researcher: i.e. after anonymisation of the text by the CPRD Operations Team.

The aspect of the work of the CPRD is covered by the REC approval granted by the National Research Ethics Service of the Health Research Authority and Section 251, CAG approval.

6.2.7. Using CPRD GOLD data for public health research

The CPRD GOLD database 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 CPRD 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, pharmacoeconomics and health service planning) are becoming more common. Since 1988, in excess of 900 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

[3] 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

MMR vaccine and autism, and selective serotonin reuptake inhibitors (SSRIs) and self-harm/suicide.

6.2.8. Linkage of CPRD GOLD to external data sources

In 2007, CPRD began an initiative to link CPRD GOLD data to a number of external data sources to enhance the research capacity of the database. This linkage has been undertaken in English practices only. External data sources that have been linked include:

- Hospital Episode Statistic (HES)
- The Cancer Registry
- ONS Mortality Data
- The Myocardial Ischaemia National Audit Project (MINAP)
- Indices of Deprivation (Townsend scores and Index of Multiple Deprivation)
- ALSPAC
- National Joint Registry
- Hospital Treatment Insights (HTI)

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

Annex 1 - Membership and member biographies

Professor Patrick Waller BMedSci MD MPH FRCP Ed. FFPM FBPharmacolS (Chair)
Honorary Professor, Faculty of Epidemiology and Public Health, London School of Hygiene and Tropical Medicine

Professor Jacqueline Cassell FFPH FRCP MD MSc DipGUM DFFP (Deputy Chair)
Professor of Primary Care Epidemiology, Brighton and Sussex Medical School

Dr Krishnan Bhaskaran MSc PhD
Lecturer in Statistical Epidemiology, Department of Non-Communicable Diseases Epidemiology, London School of Hygiene and Tropical Medicine, London

Dr Benjamin Cairns BA BSc PhD
Statistical Epidemiologist, Cancer Epidemiology Unit, University of Oxford

Dr Christopher Edwards BSc (Hons) PhD MIPEM
Consultant Medical Physicist, Aneurin Bevan Health Board, St Woolos Hospital in Newport, South Wales

Professor Martin Gulliford MA FRCP FFPH
Professor in Public Health at King's College London

Dr Iskandar Idris BMedSci BMBS FRCP (London & Edin) DM
Associate Professor in Diabetes and Honorary Consultant Physician, University of Nottingham & Royal Derby Hospital

Professor Peter Helms MBBS PhD FRCP FRCPCH FFSEM
Professor of Child Health, University of Aberdeen

Dr Umesh T Kadam MRCGP MPhil MSc PhD FFPH
Senior Lecturer in General Practice/Epidemiology, Keele University, Staffordshire

Professor Benjamin A. Lipsky MD FACP FIDSA FRCP
Deputy Director, Graduate Entry Course, University of Oxford Medical School

Ms Sally Malin BA (Hons); MA (Cantab); MSc (Econ) (Lay member)

Professor Richard Martin BMedSci BM BS MRCGP FFPH MSc PhD
Professor in Clinical Epidemiology, School of Social and Community Medicine, University of Bristol

Professor Simon Mitchell MD MRCP FRCPCH DCH DRCOG
Consultant Neonatologist, Newborn Intensive Care Unit, St Mary's Hospital, Manchester

Ms Marcia Saunders BA MA MSc (Lay member)
Chair, North West London Local Education and Training Board

Dr Richard Stevens BA MSc PhD
Senior Statistician, Nuffield Department of Primary Care Health Sciences, University of Oxford

Dr Ruben Thanacoody MD FRCP (Edin)
Senior Lecturer in Clinical Pharmacology, University of Newcastle-upon-Tyne

Member Biographies

Professor Patrick Waller is an Honorary Professor in the Faculty of Epidemiology and Public Health at the London School of Hygiene and Tropical Medicine. After graduating in medicine from Sheffield University in 1980, he trained in clinical pharmacology and epidemiology. From 1988-1990 he was Senior Research Fellow at the Drug Safety Research Unit in Southampton. He then moved to the Medicines Control Agency in London where he became Head of the Pharmacovigilance Assessment Group. From 1998-2000 he was a UK delegate to the EC's drug regulatory committee and Chairman of its Pharmacovigilance Working Party. From 2002-11 he was an independent consultant in pharmacovigilance and pharmacoepidemiology.

Professor Jackie Cassell is Director of Research, Chair in Primary Care Epidemiology, Honorary Consultant in Public Health, Brighton and Sussex Medical School. She leads a multidisciplinary programme of research funded by the Wellcome Trust on the production of electronic data and analysis of free text. Jackie is editor of the journal Sexually Transmitted Infections and serves on the Scientific Advisory Group to the MRC Methodology Research Panel. 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 Krishnan Bhaskaran is a Lecturer in Statistical Epidemiology at the London School of Hygiene and Tropical Medicine. He graduated from Sheffield University with a BSc Hons in Mathematics in 1999. After taking an MSc in Medical Statistics at Leicester University in 2000-2001, he joined the MRC Clinical Trials Unit, and stayed there for six years, working on a variety of HIV trials and observational studies, with an emphasis on HIV seroconverters (individuals with well estimated dates of HIV infection). In October 2010, on gaining his PhD at LSHTM for a project looking at environmental risk factors for heart disease, he joined the Department of Non-Communicable Diseases Epidemiology as a lecturer. He currently holds a National Institute for Health Research postdoctoral fellowship and is investigating questions around cancer pharmacoepidemiology using routinely collected healthcare data. He teaches on the LSHTM MSc Epidemiology and is the course director for the LSHTM Short Course in Practical Pharmacoepidemiology. He also teaches basic statistics to undergraduate UCL medical students.

Dr Benjamin Cairns is a Senior Statistical Epidemiologist in the Cancer Epidemiology Unit at the University of Oxford. He studies the causes of cardiovascular diseases and cancer, mostly in the Million Women Study, a study of the health and lifestyle of more than a million UK women. He also teaches statistics and epidemiology in the University of Oxford's undergraduate Medical Sciences and postgraduate Global Health programmes.

Dr Christopher Edwards obtained a first degree in Health Physics, then spent a brief time in industry as a Nuclear Power instrumentation Engineer. He then obtained a PhD in high frequency ultrasound for skin imaging from the University of Manchester Institute of Science and Technology. This was followed by 15 years as a research

lecturer in Skin Bioengineering in the Dermatology department of the University of Wales College of Medicine. Here his post involved the design, construction and use of instruments to measure skin properties, and he had a special interest in photobiology of the skin. He gained much experience in the design, running and analysis of clinical research trials. For the last 14 years he has run the phototherapy service in Newport, and has continued his research into phototherapies, while continuing to develop the popular Newport Phototherapy Course. He is a member of the Radiation Protection Special Standing Advisory Group, a Welsh Assembly Government advisory sub-committee. He is a committee member of the British Photodermatology Group and is co-author on the national guidelines on minimum standards for phototherapy and ultraviolet dosimetry in phototherapy. He is Health Board lead for research education and advises on research methodologies and statistics. He chairs the Intellectual Property Group. He is the Laser Protection Advisor to Aneurin Bevan Health Board.

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

Dr Iskandar Idris is an Associate Professor in Diabetes and Vascular Medicine at the University of Nottingham and Honorary Consultant Physician at the Royal Derby Hospital. He is currently the Training Programme Director for Specialist Training in Diabetes and Endocrinology at the East Midlands postgraduate deanery. He has ongoing academic and research interests in the field of obesity and vascular complications of diabetes and novel strategies for managing hyperglycaemia and vascular risks in patients with diabetes. Within the University of Nottingham, he has strong research links with the Division of Vascular Medicine and the MRC arthritis UK for musculoskeletal research and ageing. He has published widely in the field of diabetes, pharmacology and vascular complications.

Professor Peter Helms is Professor of Child Health University of Aberdeen and Consultant Pediatrician in the Royal Aberdeen Children's Hospital. He contributes to a number of national and international bodies and professional organizations in the areas childhood respiratory health and disease, sports and exercise medicine, and clinical pharmacology. He is Director of the Scottish Medicines for Children Network and co Chair of the European Research Network hosted at the European Medicines Agency (Enpr-EMA). His current research interests include the early expression of respiratory illness and paediatric pharmacoepidemiology.

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

Professor Benjamin Lipsky is Deputy Director of the Graduate Entry Course at the University of Oxford Division of Medical Sciences, Teaching Associate at Green Templeton College (University of Oxford), Visiting Professor of Medicine at the University of Geneva and Professor of Medicine Emeritus at the University of

Washington. After graduating from Cornell University School of Medicine (New York) he trained in internal medicine and infectious diseases at the University of Washington (Seattle), where he was appointed to the faculty in 1978 (based at the VA Puget Sound Health Care System) and rose to Full Professor in 2000. He was an active clinician, served as an Infectious Diseases and Internal Medicine consultant, Chair of Infection Control, Hospital Epidemiologist, Director of the Primary Care Clinic and a member of the Investigational Review Board. He is now collaborating on various research projects (mainly involving diabetic foot infections) and is setting up a clinical research program at the Hospital of the University of Geneva.

Sally Malin has worked in public policy (NHS and criminal justice) for over 30 years in strategic, academic and operational roles. She chaired Barnet PCT 2003-8. Currently Independent Board Member of Health Education North West London; also Lay representative on Health Education England Medical Advisory Group; on the MBBS 2020 Curriculum Committee, King's College London; and on the Credentialing Working Group, General Medical Council.

Professor Richard Martin is Professor in Clinical Epidemiology, School of Social and Community Medicine, University of Bristol and Honorary Consultant in Public Health at North Bristol NHS Trust. 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.

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 and Chair of Central Manchester Research Ethics Committee.

Marcia Saunders is Independent Chair of Health Education North West London (Local Education and Training Board). Previously a PCT and SHA chair, her main career was in social services senior management and policy analysis. She is a member of the Governors and Pro Chancellor of De Montfort University, a lay assessor for the General Medical Council, and an honorary member of the Royal Pharmaceutical Society. She holds degrees from Cornell University, the University of Chicago and Bristol University.

Dr Richard Stevens is deputy director of the statistics group at the Nuffield Department of Primary Care Health Sciences (NDPCHS) in Oxford, and a fellow of Kellogg College, Oxford. His previous experience includes eight 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 three years with the Cancer Research UK Epidemiology unit, where he studied pancreatic cancer in the Million Women Study cohort. His current research interests are in statistical models for the monitoring of chronic diseases such as diabetes, hypertension and chronic kidney disease.

Dr Ruben Thanacoody is Consultant Physician, 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 members

- Provide formal and informal advice to MHRA between meetings. Applications will be circulated electronically to ensure they are reviewed within 14 days and most CPRD 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 CPRD 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.

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
CPRD	Clinical Practice Research Datalink
CPRD GOLD	The Clinical Practice Research Datalink primary care database (formerly GPRD)
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
RCP	Research Capability Programme
RCPCH	Royal College of Paediatrics and Child Health
SEAG	Scientific and Ethical Advisory Group
SPC	Summary of Product Characteristics
UK	United Kingdom
VRMM	Vigilance and Risk Management division of MHRA (formerly Post Licensing Division)
YCC	Yellow Card Centre

ANNEX 5
DECLARATION OF INTERESTS

MEMBERSHIP OF THE INDEPENDENT SCIENTIFIC ADVISORY COMMITTEE (ISAC)

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

	PERSONAL INTERESTS		NON PERSONAL INTERESTS		
MEMBER	**NAME OF COMPANY**	**NATURE OF INTEREST**	**NAME OF COMPANY**	**NATURE OF INTEREST**	**WHETHER CURRENT**
Prof Patrick Waller	None		None		
Prof Jacqueline Cassell	None		None		
Dr Krishnan Bhaskaran	None		None		
Dr Benjamin Cairns	None		None		
Dr Christopher Edwards	None		None		
Prof Martin Gulliford	None		None		
Dr Iskandar Idris	MSD, Eli Lilly, Novo Nordisk	Speaker fees, research funding, advisory board			
Prof Peter Helms	None		None		
Dr Umesh Kadam	None		None		
Prof Ben Lipsky	Merck Innocoll Cerexa KCI Biocomposites Dipexium Debiopharm Lytix	Speaker fees Consultation fees, research funding Advisory board Advisory board Consultation fees Advisory board Consultation fees Consultation fees	None		Yes Yes No Yes Yes Yes Yes Yes
Ms Sally Malin	None		None		
Prof Richard Martin	None		None		
Prof Simon Mitchell	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/CPRD 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.