Medicines & Healthcare products Regulatory Agency

CPRD More Dimensions to Data

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

Annual Report

1st April 2016 to 31st March 2017

NHS National Institute for Health Research

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Glossary of acronyms

CAG	Confidentiality Advisory Group
CPRD	Clinical Practice Research Datalink
CPRD GOLD	GP On-Line Database (CPRD's primary care data collection database)
GP	General Practice/practitioner
HES	Hospital Episode Statistics
HRA	NHS Health Research Authority
HSCIC	Health & Social Care Information Centre (renamed NHS Digital in 2016)
ISAC	Independent Scientific Advisory Committee for MHRA Database Research
IT	Information Technology
MHRA	Medicines and Healthcare products Regulatory Agency ("the Agency")
MRC	Medical Research Council
NHS	National Health Service
ONS	Office for National Statistics
PEAG	Pharmacovigilance Expert Advisory Group (of the MHRA)
REC	NHS Research Ethics Committee
UK	United Kingdom

Foreword from the Chairman of the MHRA

I am delighted to present the 2016/17 Annual Report of the MHRA Independent Scientific Advisory Committee (ISAC). The 2016/17 period marks the first full year where the activities of the Committee have been solely related to research using anonymised data provided by the Clinical Practice Research Datalink (CPRD). Since February 2016, the review of research applications for Yellow Card data which previously fell within the ISAC's remit, has been undertaken by Pharmacovigilance Expert Advisory Group (PEAG) of the MHRA.

Reliable evidence on which to base crucial decisions informing drug safety and clinical guidance depends on access to high-quality representative population data. CPRD is an essential source of anonymised data supporting research that leads to better health outcomes for patients and for the whole population. We are indebted to GPs who recognise the importance of their role in contributing to evidence-based medicine by supplying anonymised patient data to CPRD. The range of public health studies carried out by researchers using data from CPRD is published on the CPRD website. These vital studies serve as a reminder to policy makers, healthcare professionals and the public alike of the shared benefit of having access to such high quality 'real world' information.

Each year CPRD must obtain approvals from regulatory bodies to provide anonymised data for public health research. The ISAC review of individual research applications seeking access to anonymised patient records held by CPRD is a key part of the overall governance process. Membership of ISAC is on a voluntary basis and I am very appreciative of ISAC members freely giving their time and expertise to enable CPRD to discharge its research function. Furthermore, I wish to express my gratitude to the ISAC Chair, Professor Deborah Saltman AM for her stewardship of the Committee and her tireless work to ensure all applications to CPRD have been reviewed to a high standard and in a timely manner.

Sir Michael Rawlins GBE
MHRA Chairman

Foreword from the Chair of the ISAC

Since taking office as Chair of ISAC in February 2016 I have been impressed with the work of the Committee and the support provided by CPRD. Coming from a general practice and research epidemiology background, I understand the importance of CPRD and health data and am delighted to Chair such a diligent and devoted Committee. The twelve months covered by this report has continued to see a steady year-on-year increase in the number of new research protocols considered by the Committee. During this period, we have reviewed a total of 309 new research protocols and an additional 77 amendments and resubmissions, compared with 329 applications in the 15-month period covered by our previous report. This increase demonstrates both the importance of the database and research services provided to public health researchers and the efficiency of the Committee and supporting CPRD team. What's more ISAC reviewed applications from researchers based all over the world, including Canada, the United States and Europe, demonstrating that the ISAC is able to help support and inform public health across the world.

I would like to welcome two new scientific members to the Committee: Mrs. Rosie Cornish and Dr. Evangelos Kontopantelis. The scrutiny of research applications is dependent on the voluntary contributions of the ISAC members. I would like to thank them for their interest in the work of the Committee, and indeed thank all members of the Committee for their continuing contributions to the quarterly ISAC meetings and the review of research protocols submitted to the ISAC for consideration. I would like to share my thanks to three parting members of the Committee who completed their term of office during the period of this report: Professor Umesh Kadam, Dr. Benjamin Lipsky and Professor Simon Mitchell. Their longstanding contributions to the success of the Committee, and in safeguarding UK public health, have been integral to the ISAC's achievements.

I would also like to recognise the excellent support we have received from CPRD, its Observational Research and Secretariat staff, throughout the year. In particular, I would like to thank the CPRD Director Dr. Janet Valentine for her continued support and the dedication and hard work of Ms. Tarita Murray-Thomas, CRPD Senior Researcher, and Mr Daniel Brett, CPRD Research Applications Officer, providing the primary Secretariat support function for the Committee and administrative support in the management and review of research applications. I look forward to working closely with the ISAC membership and CPRD team in 2017/18.

Professor Deborah Saltman AM

Chair, Independent Scientific Advisory Committee (ISAC)

1. Introduction and background

1.1. Introduction to the report

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 Clinical Practice Research Datalink (CPRD) is a governmental, not-for-profit research service, jointly funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA).

The role of the Independent Scientific Advisory Committee for MHRA Database Research (ISAC) is to review the scientific merit of proposals for research using data from the CPRD database, including primary care data linked to other health-related data sets.

This Annual Report presents an overview of the purpose, governance, management of activities and outputs and membership of the Committee, for the period 01 April 2016 to 31 March 2017.

A description of the data and its uses are outlined below in Section 1. Details of the ISAC's governance and function are described in Section 2. An analysis of research applications considered and approved by the Committee is provided in Section 3, "Activities & Outputs".

1.2. Clinical Practice Research Datalink

1.2.1. CPRD database services

CPRD's research services are based on a database of longitudinal, anonymised primary care records collected from GP practices across the four UK nations. The primary care database built and managed by CPRD is called GOLD (GP On-Line Database). At the end of this reporting period, the database held research quality data on 15 million patients. To extend the utility and value of the data for public health research, the primary care data are linked to other datasets.

CPRD data are used for public health research both nationally and internationally by researchers in academic institutions, regulatory agencies, the NHS, Government organisations and the pharmaceutical industry. Research using CPRD data encompasses disease epidemiology, drug

safety, pharmacoepidemiology, drug utilisation, treatment patterns, health outcomes, pharmacoeconomics and health service planning. Since 1988, over 1,700 research papers using CPRD data have been published in a wide variety of peer-reviewed scientific journals. These include studies that have contributed to the development of clinical guidelines on important public health issues such as measles, mumps and rubella (MMR) vaccination and selective serotonin reuptake inhibitors (SSRIs).

1.2.2. Permissions and approvals

CPRD must seek annual approval from a NHS Health Research Authority (HRA) Research Ethics Committee (REC) to enable CPRD to collect and release anonymised primary care data for observational research.

In addition, CPRD must seek annual Section 251 approval from the HRA Confidentiality Advisory Group (CAG) to enable linkage of primary care patient data with other health-related data in England, without breaching the common-law duty of confidentiality.

CPRD operates a General Practitioner (GP) opt-in model, whereby a GP practice consents to contribute their anonymised patient records to CPRD. In England, a GP practice may also give permission for their data to be linked to other health-related datasets. GPs are provided with Fair Processing Notices to inform patients of the right to opt-out of their data being shared with CPRD for research purposes.

CPRD must also annually complete the NHS Toolkit assessment and has a data sharing agreement with NHS Digital to enable data linkage services.

Relevant ethical and regulatory permissions must also be obtained by custodians of datasets seeking to link to primary care data.

1.2.3. Data collection

CPRD manages the collection of data from GP practices that use the Vision Primary Care System software or the EMIS GP Clinical System software. Once a practice has agreed to contribute data to CPRD, data are transferred to CPRD in an encrypted form via a secure N3 connection. On arrival, the data are verified for integrity and completeness before further processing and anonymisation.

1.2.4. Anonymisation process

CPRD data contains anonymised coded patient level data. No data that can directly identify patients such as names, addresses, full date of birth and NHS number, are transmitted to or held by CPRD. This ensures that the identity of individuals within the database cannot be established by anyone within CPRD or by researchers using CPRD data.

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 can be added to their longitudinal record. To achieve this, every patient is allocated an encrypted 'flag' by the GP system software. The GP is able to re-identify individual patients using this 'flag' however it is not possible for anyone outside the practice to use the 'flag' for patient identification. To further protect patient identity, the identities of individual practices are also encrypted so that researchers are unable to determine which practices are contributing data to CPRD. The GP system software provider also anonymises doctors and practice staff who enter data into their system. As an additional privacy safeguard, the patient 'flag' and practice number are encrypted again within CPRD before the anonymised data is supplied to researchers.

1.2.5. Data linkage

NHS Digital is the statutory body in England permitted to receive identifiable patient data. NHS Digital provide a linkage service for CPRD enabling GOLD (primary care) data from consenting English GP practices to be linked to other health-related data sources.

The datasets routinely linked to CPRD primary care data during this reporting period were:

- Hospital Episode Statistics (HES)
    - Admitted Patient Care data
    - Outpatient data
    - Accident & Emergency data
    - Diagnostic Imaging Dataset
- Cancer Registry (Public Health England)
- ONS Death Registration Data
- Indices of Deprivation (Townsend scores and Index of Multiple Deprivation)

2. Governance and Review of Research Applications

2.1. Role of the ISAC including Terms of Reference

The ISAC was established by the Secretary of State for Health in February 2006 to review proposals for research using data from the MHRA's CPRD and Yellow Card Scheme databases. Since February 2016, the review of Yellow Card Scheme applications has moved to the Pharmacovigilance Expert Advisory Group (PEAG), with ISAC reviewing protocols for CPRD's data and research services only.

The Terms of Reference of the ISAC are to:

- Consider and provide advice to the MHRA on the feasibility, quality and public health value of research studies proposing use of anonymised patient level data from the CPRD.
- Provide timely and high-quality peer reviews on the scientific (medical, epidemiological, methodological) merit of research protocols proposing access and use of CPRD data.
- Highlight important ethical or confidentiality issues that may arise during access and/or use of CPRD data in research studies, taking into consideration input from the Confidentiality Advisory Group or research ethics committees.
- Advise on, and contribute to, the scientific content of guidance relating to the development of research protocols proposing access and use of data from CPRD.
- Review internal workings of the Committee to ensure consistency, efficiency and high standards of peer-review are maintained.
- Advise on other specific issues as requested by the MHRA and/or CPRD.

2.2. Membership

The ISAC membership falls into two key categories: scientific and lay members. Scientific members provide advice on the medical, statistical/epidemiological and methodological aspects of protocols submitted to the Committee for review. Lay members provide advice on protocols seeking additional information from GPs, patients and practices, and where there may be potential governance issues associated with a study.

2.2.1. Membership over the reporting period

At the end of the reporting period, ISAC membership consisted of 19 scientific members, including the Chair, and 2 lay members. A total of 24 members served on the Committee, inclusive of membership turnover (i.e. members whose terms of office ended, members whose terms were renewed, and new

appointees to the ISAC). Lay membership remained constant with two members on the Committee throughout the reporting period. Membership of the ISAC between 1 April 2016 and 31 March 2017 is listed in Annex 1.

2.2.2. Appointment of members

ISAC members are appointed directly by the MHRA. New members are appointed for an initial two-year term, which may be extended for a further two years, to a maximum four-year appointment. The duties of the ISAC members are be found in Annex 2.

2.2.3. Declarations of interest

Members of the ISAC are required to declare any relevant interests or relationships with the pharmaceutical industry and any other interests that may affect their impartiality or be perceived as doing so. Declarations must include interests of their immediate family members (e.g. spouse). Declarations must be made on appointment and the MHRA must be notified immediately of any changes. Failure to comply may result in removal of an individual from the Committee.

Furthermore, members are asked to declare any potential conflicts of interest relevant to individual protocols at the time of protocol review. This allows interests to be taken into account during protocol evaluation, 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. The Deputy Chair is responsible in cases where the Chair has a direct conflict of interest or is unavailable. A register of Committee member declared interests can be found in Annex 3.

2.3. Meetings of the Committee

2.3.1. Physical meetings

Formal Committee meetings, where members meet in person are held quarterly. Over the reporting period, the Committee met four times on the following dates: 13 April 2016, 13 July 2016, 19 October 2016, and 17 January 2017. The ISAC meetings were held at the MHRA offices located at 151 Buckingham Palace Road, Victoria, London SW1W 9SZ.

2.3.2. Member meeting expenses

Members are entitled to claim a set fee for each physical meeting attended. In 2016 and 2017 Committee members were entitled to claim £174 for preparation and attendance per meeting. In addition, members are entitled to claim travel and subsistence expenses as for the following:

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

The Chair is remunerated by the MHRA on a pro-rata basis for ISAC duties and does not receive payment or expenses for ISAC meeting attendance.

2.3.3. Virtual working between meetings

Review of almost all CPRD research protocol submissions was performed virtually on a continuous basis throughout the reporting period. Reviews were undertaken by ISAC members and CPRD staff and are described further in section 2.5. All phases of protocol review were overseen and signed off by the ISAC Chair.

2.4. Secretariat

The ISAC Secretariat, consisting of Agency employees, manages the processing and review of research protocol requests for access to CPRD data and provides administrative support for the Committee.

2.5. Review of research protocols

Researchers request access to CPRD data by submitting a protocol application form to the ISAC Secretariat. The ISAC Secretariat assesses each submission for completeness and once validated each application is sent on to the CPRD Observational Research team, who perform an initial assessment of the application's feasibility and a screening for risks relating to the proposed research. The application and Observational Research team assessment is then passed to the Committee for review.

When reviewing CPRD protocols, the Committee considers whether:

- The CPRD database is a suitable database with which to conduct the research;

- There are no major scientific concerns with the medical, statistical, epidemiological or methodological aspects of the study:
    - The methodology is considered appropriate, including consideration of possible bias and confounding;
    - 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 ISAC Chair receives the reviews of each protocol and makes an assessment to approve, reject or request a resubmission of the protocol. The decision is communicated to the applicant, along with appropriate feedback and comments where necessary. In cases where a resubmission is required, the applicant must respond to the reviewer's feedback in a re-submitted application. All resubmissions are reassessed by the ISAC Chair and the final decision communicated to the applicant.

2.6. Appeals process

If applicants disagree with the outcome of an ISAC decision and this cannot be resolved by minor revision of the application or by resubmission, applicants can appeal the Committee's decision. The details of the appeal process can be found in Annex 4.

2.7. Transparency of ISAC approved research protocols

Since July 2015 it has been Agency policy to publish summary information about each ISAC-approved research protocol on the CPRD website. Information is published a minimum of three months after applicants receive the approved data for their research. Further information on the ISAC approved studies can be found at https://www.cprd.com/ISAC/datause.asp.

2.8. Publication of ISAC approved studies

The findings of many studies approved by the ISAC are published in peer-reviewed scientific journals. A comprehensive list of all publications using or referencing CPRD data can be found on the CPRD website: https://www.cprd.com/bibliography/.

2.9. Publication of the ISAC activities

Summary minutes of ISAC meetings are published on both the CPRD and MHRA websites once the full minutes have been agreed by the Committee. The summary of ISAC minutes are available at https://www.cprd.com/ISAC/Minutes.asp.

The annual reports of the ISAC are made available on both the MHRA and CPRD websites, at https://www.gov.uk/government/groups/independent-scientific-advisory-committee-for-mhra-database-research and https://www.cprd.com/ISAC/Minutes.asp.

3. Activities and Outputs

3.1. Summary of applications and approvals for use of CPRD data

During the reporting period, a total of 386 applications were considered by the ISAC. Of those, 309 were new applications requesting access to CPRD data and 77 were resubmissions or amendments to protocols which were initially submitted prior to the reporting period. Of the 77 resubmissions, 68 were approved and nine were rejected.

Of the 309 new applications considered over the course of the reporting period, 242 protocols were approved, 5 were rejected or withdrawn and 62 required resubmission for consideration in the next reporting period.

Table 1 presents a breakdown of the 242 new research protocols approved by the ISAC, categorised by the Chief Investigator's organisational affiliation. The table shows that the majority of protocols were submitted by researchers based in academic organisations.

Table 1: Number of approved protocols by Chief Investigator's organisational affiliation, 2016/17

Chief Investigator's Organisational Affiliation	No. of approved protocols (n = 242)	Percent of total approved
Academia	177	73%
Pharmaceuticals	29	12%
Research Services	26	11%
Government	7	3%
National Health Service	3	1%

Table 2 provides an overview of the 242 new approved protocols categorised by study type. A protocol may be assigned to more than one study type.

Table 2: Breakdown of approved protocols by study type, 2016/17

Study Type	Count[1]
Disease Epidemiology	123
Drug Utilisation	55
Drug Safety	54
Health/Public Health Services Research	53
Drug Effectiveness	20

3.2. Protocol applications including requests for linkage to other datasets

The value of research using primary care data can be significantly augmented by linking to other data sources. Of the 242 new protocols approved by ISAC during the year, 184 (76%) included requests to link to other datasets. Table 3 presents the number of approved protocols which requested data linked to primary care data. Many protocols request linkage to more than one dataset. The most common linkage approved was for data from the Hospital Episode Statistics (HES) Admitted Patient Care dataset.

Table 3: Number of approved linkages to other health-related datasets, 2016/17

Other health data approved for release	No. of linkages approved by ISAC[2]
HES – Admitted Patient Care	160
Patient Index of Multiple Deprivation	116
Practice Index of Multiple Deprivation	111
Death Registration Data – ONS	106
HES – Outpatient	44
Patient Townsend	17
Cancer Registry	11
HES – Accident and Emergency	10
Mother and Baby Link	9
Myocardial Ischaemia National Audit Project	6
HES – Diagnostic Imaging Dataset	2
Other datasets	7

[1] The total count of study types is greater than the total number of 242 protocols approved, due to some lead investigators listing more than one study type for a protocol

[2] The total number of linkages requested exceeds the number of approved protocols, due to many protocols requesting multiple linkages

Annex 1 – Membership over 2016/17 and member biographies

Professor Deborah Saltman AM (Chair) MBBS MD MRCGP FRACGP FAFPHM GAICD. (Appointed as Chair on 18 January 2016)

Professor Richard Stevens (Deputy Chair) BA MSc PhD (Appointed as Deputy Chair in April 2016)
Associate Professor, Medical Statistics Group, Nuffield Dept of Primary Care Health Sciences, University of Oxford

Dr Angelyn Bethel MD (Appointed 1 January 2016)
Deputy Director, University of Oxford Diabetes Trials Unit

Dr Krishnan Bhaskaran MSc PhD (Reappointed 2 January 2016)
Associate Professor in Statistical Epidemiology, Department of Non-Communicable Diseases Epidemiology, London School of Hygiene and Tropical Medicine, London

Professor Sinead Brophy BSc PhD (Appointed 14 December 2015)
Professor of CIPHER, College of Medicines, Swansea University

Dr Benjamin Cairns BA BSc PhD (Reappointed 2 January 2016)
Senior Statistical Epidemiologist, Cancer Epidemiology Unit, University of Oxford

Mrs Rosie Cornish (Appointed 17 January 2017)
Senior Research Associate, School of Social and Community Medicine, University of Bristol

Dr Christopher Edwards BSc (Hons) PhD MIPEM (Reappointed 2 January 2016)
Consultant Medical Physicist, Aneurin Bevan University Health Board, St Woolos Hospital in Newport, South Wales

Dr Duncan Edwards BSc, MB BS, MRCGP (Appointed 1 January 2016)
NIHR Doctoral Research Fellow and GP, Department of Public Health and Primary Care, The School of Clinical Medicine, University of Cambridge

Professor Peter Helms MBBS PhD FRCP FRCPCH FFSEM (Reappointed 1 January 2015)
Emeritus Professor of Child Health, University of Aberdeen

Dr Caroline Jackson BSc, MSc, PhD (Appointed 1 January 2016)

Chancellor's Fellow, Institute of Population Health Sciences and Informatics, University of Edinburgh

Professor Umesh T Kadam MRCGP MPhil MSc PhD FFPH (Retired as a member on 14 November 2016)

Professor of Health Services Research & Clinical Epidemiology, Keele University, Staffordshire

Dr Wendy Knibb MSc (Econ.) PhD (Health Econ.) (Appointed 1 October 2014)

Independent Health Economics consultant

Dr Evangelos Kontopantelis PhD (Appointed 1 January 2017)

Reader in Biostatistics and Health Services Research, The Farr Institute for Health Informatics Research, University of Manchester

Professor Benjamin A Lipsky MD FACP FIDSA FRCP (Reappointed 1 January 2015)

Deputy Director, Graduate Entry Course, University of Oxford Medical School

Ms Sally Malin BA (Hons) MA (Cantab) MSc (Econ) (Lay member) (Reappointed 2 January 2016)

Dr Emily McFadden MA (Cantab) MSc PhD (Appointed 1 October 2014)

Senior Statistical Epidemiologist – Nuffield Department of Primary Care Health Sciences, University of Oxford

Professor Simon Mitchell MD MRCP FRCPCH DCH DRCOG (Retired as a member on 14 November 2016)

Consultant Neonatologist, Newborn Intensive Care Unit, St Mary's Hospital, Manchester

Professor Keith Neal (Appointed 1 October 2014)

Emeritus Professor in the Epidemiology of Infectious Diseases, University of Nottingham and Consultant Epidemiologist, for the Field Epidemiology Service, Public Health England

Dr Jennifer Quint PhD (Appointed 15 December 2015)

Clinical Senior Lecturer Respiratory Epidemiology, National Heart and Lung Institute, Imperial College London

Ms Marcia Saunders BA MA MSc (Lay member) (Reappointed 29 November 2014)

Chair, Health Education England North West London Local Education and Training Board (to August 2017); Chair, Tribunals Advisory Committee, Health and Social Care Professions Council (from April 2017)

Professor Sara Thomas PhD (Appointed 1 December 2015)

Professor of Infectious Disease Epidemiology at the London School of Hygiene and Tropical Medicine

Dr Hester Ward (Appointed 1 January 2016)

Consultant in Public Health Medicine (Health Informatics)

Professor Ian Wong (Appointed 14 December 2015)

Chair in Pharmacy Practice, UCL School of Pharmacy.

Member biographies

Professor Deborah Saltman AM is the Chair of the ISAC. Previously she was a clinical and scientific advisor and consultant within the medical communications and pharmacoeconomics arena. She holds positions as Honorary Professor in the Faculty of Medicine at Imperial College and the University of Sydney and is Visiting Professor at the University of Technology, Sydney. She has extensive experience in databases and database research, HTA assessments, health research, postgraduate medical education and medical publishing.

Deborah was made a member of the Order of Australia in 2004, and is a recipient of the Rose Hunt Medal from the RCGP (UK 2006). She is also a Notable Australian Doctor and has a doctorate in general practice as well as Fellowships of the RACGP, RCGP, RACP (Public Health Faculty). She is also a graduate of the Australian Institute of Company Directors. An active member of several professional organisations, Deborah is currently working with the UK Council of Psychotherapists to develop a new Code of Ethics.

Professor 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. He is course director of the M.Sc. course in Evidence Based Health Care Medical Statistics at the University of Oxford.

Dr Angelyn Bethel is Associate Professor of Diabetes and Endocrinology at the University of Oxford and is the Deputy Director of the University of Oxford Diabetes Trials Unit (DTU), a fully registered UKCRC Clinical Trials Unit and an internationally recognised Academic Research Organisation. At the DTU, she provides clinical and strategic oversight for ongoing multicentre cardiovascular outcomes trials in diabetes. Dr. Bethel is the primary investigator for GLINT, has served as the Academic Clinical Lead for Trial Evaluating Cardiovascular Outcomes with Sitagliptin, EXenatide Study of Cardiovascular Event Lowering, and Acarbose Cardiovascular Evaluation and has worked closely with the Translational Research Group at DTU, serving as a primary investigator and clinical advisor for a wide range of early phase clinical studies.

Dr Krishnan Bhaskaran is an Associate Professor in Statistical Epidemiology and Sir Henry Dale Fellow, working on cancer survivorship and pharmacoepidemiology within the Electronic Health Records Research group at the London School of Hygiene and Tropical Medicine.

Professor Sinead Brophy is Professor of Public Health Informatics at Swansea University. She has over 20 years of experience working with large data sets and linkage of routine data for digital epidemiology, and longer term follow-up of interventions and natural experiments. She is Deputy Director of the National Centre of Population Health and Wellbeing and Lead of Informatics, Pharmacoepidemiology lead (CIPHER – Centre for the Improvement of Population Health through E-records Research) within the FARR Institute. She also has expertise in developing electronic cohort studies.

Dr Benjamin Cairns is a Senior Statistical Epidemiologist in the Nuffield Department of Population Health at the University of Oxford. He is currently funded by the British Heart Foundation Centre of Research Excellence, Oxford, for research into aortic valve disease in large health and lifestyle studies such as the Million Women Study and UK Biobank. He is an epidemiology module lead and statistics tutor for the University of Oxford's MSc in Global Health Science programme.

Mrs Rosie Cornish is a statistical epidemiologist. She has been in the School of Social and Community Medicine at the University of Bristol since 2007. During that time, she has mainly been involved in projects using routine health data including, since 2011, the Project to Enhance ALSPAC through Record Linkage. In 2014 she obtained an MRC fellowship to investigate how linkage to administrative and routine health data could be used to understand and reduce bias due to missing data and measurement error in observational studies; this mainly uses data from ALSPAC but she is also collaborating with colleagues at the Norwegian Institute of Public Health using data from the Norwegian Mother and Child Cohort Study. Within this, she is particularly focussing on mental health outcomes – including anxiety and depression, self-harm, ADHD and conduct disorder. This work is being done in association with the Farr Institute and uses data from the National Pupil Database, Hospital Episode Statistics datasets, CPRD and other linked primary care data.

Dr Christopher Edwards is a consultant medical physicist and he runs the ultraviolet phototherapy service in the Aneurin Bevan University Health Board. He undertakes translational research into Ultraviolet phototherapies and is co-author of UK National Guidelines for Phototherapy and for Dosimetry in UV Phototherapy. He is the Health Board advisor in research methodologies and medical statistics. He is a topic Expert to the NICE Guideline Update for Neonatal Phototherapy and a member of the panel of Expert Advisers for the Centre for Clinical Practice at NICE.

Dr Duncan Edwards is an NIHR Doctoral Research Fellow at the University of Cambridge and GP in South Norfolk. He graduated from Royal Free and University College London Medical School in 2005. After working as a junior doctor in London and East Anglia, he undertook general practice training combined with an academic clinical fellowship at the University of Cambridge between 2007 and 2011 before he joined Grove Surgery, Thetford as a GP partner in 2011. From 2013-5 he was a board member of South Norfolk CCG. His own research is focused on the prevention and treatment of stroke and cardiovascular disease in the primary care setting.

Professor Peter Helms is Emeritus Professor of Child Health University of Aberdeen and previous Consultant Paediatrician in the Royal Aberdeen Children's Hospital. He contributes to a number of national and international bodies and professional organisations in the areas childhood respiratory health and disease, sports and exercise medicine, and clinical pharmacology. He is immediate past 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 Caroline Jackson is a Chancellor's Fellow in the Population Health Sciences and Informatics Institute at the University of Edinburgh. After graduating in Biological Sciences (Hons Immunology), she embarked on a career in epidemiology, obtaining her MSc in Epidemiology from the LSHTM and her PhD from University of Edinburgh in 2009. Her research interests include cardiovascular disease, multimorbidity (including mental and physical health co-morbidity) and health inequalities, using observational and routinely collected linked data. Prior to her current post, she was as a research associate at the University of Edinburgh, a MRC Career Development fellow with the Scottish Collaboration for Public Health Research and Policy and, most recently, a post-doctoral fellow in the School of Public Health at the University of Queensland.

Professor Umesh Kadam is a GP and clinical epidemiologist who has led the development of comorbidity and multimorbidity programmes using local, national and international databases.

Dr Wendy Knibb is a retired Senior Lecturer in Health Economics. Having graduated (1st class) in Economics with Politics, she took an MSc in Economics and subsequently a PhD in Health Economics from the University of Surrey. She has extensive knowledge of research in both Health Economics and also evaluative studies. She was seconded to the Department of Health SE part-time for 3 years (2008- 11) to advise on Health Economics and evaluative techniques. She has been an active member of the European Health Management Association for many years and has led a special interest group on their behalf. She has sat on a commissioning panel for the National Institute

for Health Research and has also chaired a NHS Research Ethics Committee. Currently, she is actively involved in some research projects within her area of interest.

Dr Evangelos Kontopantelis is a Biostatistician and Health Services Researcher, mainly working with large-scale primary care databases (PCDs) to investigate important health care issues: the effect of monetary incentives on quality of care, predictors of cancer, cancer screening utilisation, care for people with severe mental illnesses. From a methodological perspective, he is primarily interested in computational statistics, meta-analysis, time series analysis and the validity issues around large databases in health care.

Professor Benjamin Lipsky is an Associate Fellow and Teaching Associate at Green Templeton College (University of Oxford), Visiting Professor of Medicine at the University of Oxford, 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 University of Oxford and several countries around the world.

Sally Malin is a Masters' graduate with over 35 years' experience of strategy, service delivery and research in health care, social policy and criminal justice. She has extensive Board experience of leadership, governance and assurance, and excellent influencing and communication skills with a strong track record of securing improvement for public benefit.

Dr Emily McFadden is a Senior Statistical Epidemiologist in the Nuffield Department of Primary Care Health Sciences at the University of Oxford, where she also lectures in Study Design and Research Methods for the postgraduate Evidence Based Health Care programme, and in Medical Statistics for the undergraduate Medical Sciences programme. Her current research focuses on monitoring chronic conditions in primary care. She graduated from the University of Cambridge with an MA in Natural Sciences and Biological Anthropology, and from the London School of Hygiene and Tropical Medicine with an MSc in Epidemiology. She completed her PhD in 2009 at the University of Cambridge in the Department of Public Health and Primary Care. From 2009 to 2012 she worked as a Research Fellow in Epidemiology and Medical Statistics at the Institute of Cancer Research.

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 and 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.

Professor Keith Neal trained in infectious diseases and public health. After training worked as a senior lecturer in the epidemiology of infectious diseases and as a consultant for the UK public health services (Health authorities, Health Protection Agency and Public Health England) as a consultant epidemiologist for over 30 years. He was promoted to clinical professor during my career. His research interests included hepatitis C, meningococcal disease, food poisoning risks and sequelae particularly campylobacter and making surgery safer. He was involved in vaccine trials for HPV and meningitis. He delivered undergraduate and post graduate teaching on epidemiology, infectious diseases, public health and also ran the student elective project module His public health work including outbreak investigation and management, vaccine and travel advice, assessing clinical services and delivery epidemiological services of a region (5-8 million people). He represented his colleagues on the national infected health care workers advisory panel, hepatitis, meningitis and food poisoning national groups. He also contributed to the Ebola response with three visits; for the European Union, WHO and finally PHE to act as locum for the national lead.

Marcia Saunders is a lay member of ISAC. Formerly Chair of an NHS strategic health authority and primary care trusts, she is currently a performance assessor for the General Medical Council, Pro-Chancellor at De Montfort University, and Chair of the Health and Care Professions Council's Tribunals Advisory Committee.

Dr Jennifer Quint received her BSc MBBS degrees from the University of London, UK before going on to gain a PhD from University College London and an MSc in Epidemiology from the London School of Hygiene and Tropical Medicine, UoL. More recently, she became a Fellow of the Higher Education Academy and Royal College of Physicians. Dr Quint is currently Clinical Senior Lecturer of Respiratory Epidemiology at the National Heart and Lung Institute (NHLI), Imperial College London and an Honorary Consultant at the Royal Brompton Hospital. Furthermore, she leads a clinical epidemiology research group covering various areas of respiratory and cardiovascular disease. Her work centres largely on the use of electronic health records to study COPD and other chronic respiratory diseases, including bronchiectasis and asthma. The majority of this work has been on exploring both the effect of COPD exacerbations on vascular outcomes and the relationship between environmental factors and exacerbations of COPD. She partners with the Royal College of Physicians and is responsible for the analysis for the National COPD Audit and Pilot Asthma Audit. Dr Quint was awarded a COPD Rising

Star award at COPD10 in 2016 as well as being “Highly Commended” at the BMA Medical Book Awards for co-authoring the Eureka Respiratory Medicine textbook. She currently serves as educational editor and associate editor for *Thorax*, is secretary of the Epidemiology group of the European Respiratory Society and the Information Governance Trustee for the British Thoracic Society.

Professor Sara Thomas is a Professor of Infectious Disease Epidemiology at the London School of Hygiene and Tropical Medicine. Her research focuses on the epidemiology of infections, immune-mediated disorders, vaccines and disorders of pregnancy, and much of this work involves use of linked electronic health records. She currently leads the Electronic Health Records Theme of the Health Protection Research Unit in Immunisation, a research collaboration between LSHTM and Public Health England. She also teaches epidemiological methods on a number of MSc and short courses at LSHTM, and she is the Programme Content Director of the LSHTM MSc in Epidemiology by Distance Learning.

Dr Hester Ward is a Consultant in Public Health Medicine for NHS Scotland and Honorary Reader, University of Edinburgh School of Molecular, Genetic & Population Health Sciences. She has expertise in health informatics and is interested in improving population outcomes through use of health information.

Professor Ian Wong is jointly appointed by the UCL School of Pharmacy in London and the University of Hong Kong. Professor Wong is currently the Head of Research Department of Practice and Policy at UCL School of Pharmacy and the Co-Director of the Centre for Safe Medication Practice and Research at the University of Hong Kong. He served as a board member of Pharmacy and Poisons Board of Hong Kong (the regulatory agency). Professor Wong was the founding director of the Centre for Paediatrics Pharmacy Research at UCL and Great Ormond Street Hospital for Children (2002 to 2011). Prof Wong has extensive experience in using clinical research databases for pharmacoepidemiology research.

Annex 2 – Duties of ISAC members

1. 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.
2. Attend all scheduled and unscheduled meetings of the Committee.
3. 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.
4. Be able and be prepared to speak on a range of relevant issues and not just their own areas of specialism.
5. Develop an understanding of the types and uses of CPRD data, and understand how and when release of data could lead to patients being identified if applications are not robust scientifically.

Annex 3 – ISAC Members Declaration of Interests (2016/17)

	Personal Interests		Non-Personal Interests		Current Interest
Member	**Name of Company**	**Nature of Interest**	**Name of Company**	**Nature of Interest**	
Prof. Deborah Saltman AM (Chair)	None	N/A	None	N/A	
Prof. Richard Stevens	Novartis	Member of DMC committee for a trial.	None	N/A	Yes
Dr Angelyn Bethel	Boehringer Ingelheim	Consultancy (Advisory Board)			Yes
	NovoNordisk	Consultancy			Yes
	Sanofi	Consultancy			Yes
			Merck, Sharp & Dohme	Department receiving research support	Yes
			AstraZeneca	Department receiving research support	Yes
Dr Krishnan Bhaskaran	None	N/A	None	N/A	
Prof. Sinead Brophy	None	N/A	None	N/A	
Dr Benjamin Cairns	None	N/A	None	N/A	
Mrs Rosie Cornish	None	N/A	None	N/A	
Dr Christopher Edwards	None	N/A	None	N/A	
Dr Duncan Edwards	None	N/A	None	N/a	
Prof. Peter Helms	None	N/A	None	N/A	
Dr Caroline Jackson	None	N/A	None	N/A	
Prof. Umesh Kadam	None	N/A	None	N/a	

Dr Wendy Knibb	None	N/A	None	N/A	
Dr Evangelos Kontopantelis	None	N/A	None	N/A	
Prof. Benjamin Lipsky	KCI/Acelity	Consultancy	None	N/A	Yes
	Dipexium	Consultancy			Yes
	Debiopharm	Consultancy			Yes
	Microbion	Consultancy			Yes
	Genentech	Consultancy			Yes
Sally Malin	Health Education England	Patient member on Patient Advisory Forum	None	N/A	No
	King's College London	Lay member on School of Medical Education Committee			No
	General Medical Council	Lay member on Standards for Curricula and Assessments Review			No
Dr Emily McFadden	None	N/A	None	N/A	
Prof. Simon Mitchell	None	N/A	None	N/A	
Prof. Keith Neal	None	N/A	None	N/A	
Marcia Saunders	None	N/A	None	N/A	
Dr Jennifer Quint	AstraZeneca	Consultancy	None	N/A	Yes
	GlaxoSmithKline	Grants and Consultancy			Yes
	IMS Health	Consultancy			Yes
	Insmed	Grant			Yes
	Boehringer Ingelheim	Consultancy			Yes

	Chiesi Farmaceutici S.p.A	Consultancy			Yes
Prof. Sara Thomas	None	N/A	None	N/A	
Dr Hester Ward	Raptor Pharmaceuticals	Spouse: One off Advisory Board meeting attendance in 2016 (fee paid)	None	N/A	Yes
	Lamellar Biomedical Ltd	Spouse is medical advisor to the Board			Yes
	Elsevier	Spouse is editor on three medical text books (co-editor on 1)			Yes
Prof. Ian Wong	Therakind	Director and shareholder			Yes
	Healthcare Innovation Technology Service (UK)	Director			Yes
	Jacobson Pharmaceutical (Hong Kong)	Consultancy			Yes

Annex 4 – 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 CPRD ISAC Secretary. 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, 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.