Medicines & Healthcare products Regulatory Agency

CPRD

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

Annual Report

1st April 2017 to 31st March 2018

NHS National Institute for Health Research

Contents

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)
EHR	Electronic Health Record
EMIS®	Egton Medical Information Systems (rebranded under EMIS Health in July 2015)
GP	General Practice/Practitioner
HES	Hospital Episode Statistics
HRA	NHS Health Research Authority
HSCIC	Health & Social Care Information Centre (renamed NHS Digital in 2016)
IG	Information Governance
ISAC	Independent Scientific Advisory Committee for MHRA Database Research
MHRA	Medicines and Healthcare products Regulatory Agency ("the Agency")
N3	The high-speed broadband network for the NHS
NCRAS	National Cancer Registration and Analysis Service
NHS	National Health Service
ONS	Office for National Statistics
PROMS	Patient Recorded Outcome Measure
REC	Research Ethics Committee

Foreword from the Chairman of the MHRA

I am very pleased to present the 2017/18 Annual Report of the MHRA Independent Scientific Advisory Committee (ISAC). Research undertaken using anonymised data supplied by the Clinical Practice Research Datalink (CPRD) continues to provide unparalleled insights into population health and healthcare delivery. CPRD is a prized public health asset, with its high quality patient data playing an essential role in MHRA's daily medicines safety and surveillance regulatory activities. CPRD remains a leading health data resource of choice for public health studies conducted by regulators, academics and the pharmaceutical industry worldwide. The ensuing evidence which is translated into drug safety guidance and everyday clinical practice, is only possible because of anonymised patient data contributed by GP practices across the UK. I would like to express my gratitude to the growing number of GPs who recognise the benefits of supplying data to CPRD, leading to better health outcomes and quality improvements for their patient population as a result.

Details of research using CPRD data are published on the CPRD website. I believe this level of transparency is important to both educate and reassure the public about how their anonymised data are being responsibly used to safeguard and protect patient and public health. All research studies published on the website have been approved by ISAC. ISAC members voluntarily donate their time and expertise to review each research protocol requesting access to CPRD data. I am very appreciative of the significant efforts of ISAC members enabling CPRD to continue to operate within a robust governance framework. In particular, on behalf of MHRA and research community, I am extremely grateful to the ISAC Chair, Professor Deborah Saltman, AM, for her sterling leadership of the Committee and dedication to ensuring all research applications are reviewed within designated timeframes and to a high standard.

Sir Michael Rawlins GBE
MHRA Chairman

Foreword from the Chair of ISAC

Since taking office as Chair of ISAC in February 2016 I continue to be 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 have seen a further increase in the workload of the Committee. While a similar number of new research protocols have been received in this period compared to the previous report, the number of resubmissions and amendments received has increased by 36% and 54% respectively. That the Committee has shouldered this increase while at the same time reducing the average time for feedback on applications is particularly impressive. The figures reinforce both the significance of the database and research services provided to public health researchers, and the efficiency of the Committee and supporting CPRD team. Furthermore, the significant proportion of research applications requesting linkage to one or more other data sources highlights the importance of CPRD's data linkage service.

A number of ISAC members completed their membership terms during this reporting period, and I would like to extend my gratitude to our departing colleagues: Dr Krishnan Bhaskaran, Dr Benjamin Cairns, Dr Christopher Edwards, Professor Peter Helms, as well as Dr Caroline Jackson and Dr Angelyn Bethel. The important contributions offered by these members has been invaluable in the protecting and safeguarding of UK public health. I would also like to welcome the 8 new members to the Committee. The success of the ISAC is dependent on the voluntary contributions offered by members and I would like to thank them for their interest in the work of the Committee, and indeed thank all members for their continuing contributions to the quarterly ISAC meetings and the review of research protocols.

I would also like to recognise the excellent support we have received from CPRD, its Observational Research and Secretariat staff. In particular, I would like to thank the CPRD Director Dr. Janet Valentine for her continued support, Dr. Puja Myles, Head of Observational Research, Ms. Tarita Murray-Thomas, CRPD Senior Researcher, as well as Mr Jonathan Lind, Mr Daniel Brett, and Mr Sam Speer, who provide 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 2018/19.

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 UK government, not-for-profit research service, jointly supported by the National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA), supplying anonymised health data for public health research.

The role of the Independent Scientific Advisory Committee for MHRA Database Research (ISAC) is to assess the public health benefits and scientific merit of proposals for research seeking to use 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, outputs and membership of the Committee, for the period 01 April 2017 to 31 March 2018.

A description of the data and its uses are outlined below in Section 1. Details of 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

The CPRD database offers a quality-assured source of longitudinal, near real-time health data that is representative of the UK population, for epidemiological and pharmacoepidemiological research. CPRD data are used worldwide by regulators, academic researchers and the life science industry for observational and electronic healthcare record (EHR) enabled interventional public health studies. Approximately 2,000 peer-reviewed articles using CPRD data have been published to date. These include studies that have contributed to the development of best practice and clinical guidelines on important public health issues such as demonstrating the safety of the measles, mumps, and rubella (MMR) vaccination and the protective benefits for newborns of administering the whooping cough vaccine to expectant mothers during pregnancy.

CPRD data are sourced from a UK-wide network of over 1,100 primary care practices across the UK and the database includes more than 22 million patient lives, of which 5 million are currently registered patients at contributing GP practices, with data including a median follow-up time of nearly 10 years.

The CPRD database contains coded and anonymised EHR data from primary care practices capturing information on:

- Demographic data
- Diagnoses and symptoms
- Drug exposures
- Vaccination history
- Laboratory tests
- Referrals to hospital and specialist care

1.2.2. Safeguarding patient data

CPRD must seek annual approval from an NHS Health Research Authority (HRA) Research Ethics Committee (REC) to enable CPRD to collect and release anonymised primary care data for observational research. [REC reference number: 05/MRE04/87]

Each year CPRD obtains Section 251 regulatory support through the Confidentiality Advisory Group for NHS Digital to process patient data on behalf of CPRD, allowing CPRD to supply anonymised linked data for public health research. [CAG reference number: ECC5-05(a)/2012]

CPRD also completes an annual IG Toolkit.

CPRD operates a GP opt-in model, whereby a GP practice consents to contribute their anonymised patient records to CPRD. 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.

1.2.3. Data collection

CPRD manages the collection of data from GP practices that use the Vision® Primary Care System software (contributing to the CPRD GOLD database) or the EMIS® GP Clinical System software (contributing to the CPRD Aurum database). Once a practice has agreed to contribute data to CPRD, de-identified data are transferred to CPRD in an encrypted form via a secure N3 connection. On receipt, 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 ever held by CPRD. The identity of individuals within the database cannot be established by anyone within CPRD or by researchers using CPRD data.

In order to update individual patient records on an ongoing basis, every patient and practice within the database must be uniquely distinguishable, to enable new information about a specific patient to be added to their longitudinal record. To achieve this, every patient is allocated an encrypted patient-level record code by the GP system software. The GP is able to re-identify individual patients using this record code, however it is not possible for anyone outside the practice to use the record code 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 records relating to doctors and practice staff who enter data into their system. As an additional privacy safeguard, the patient record code and practice number are encrypted again within CPRD before the anonymised data is supplied to researchers.

1.2.5. Data linkage

NHS Digital, legally known as Health and Social Care Information Centre (HSCIC), is the statutory body in England permitted to receive identifiable patient data. NHS Digital provide a linkage service for CPRD enabling data from consenting English GP practices to be linked to other health-related data sources while upholding patient confidentiality. CPRD has data sharing agreements with NHS Digital and Public Health England to enable data linkage services.
The datasets routinely linked to CPRD primary care data during this reporting period are listed in Section 3.2.

2. Governance and Review of Research Applications

2.1. Role of ISAC including Terms of Reference

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 maintaining responsibility for reviewing protocols to access CPRD's data and research services.

The Terms of Reference of 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

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 ethical issues associated with a study.

2.2.1. Membership over the reporting period

At the end of the reporting period, ISAC membership consisted of 25 scientific members, including the Chair, and 2 lay members. A total of 31 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 ISAC). Lay membership remained constant with two members on the Committee throughout the reporting period. Membership of ISAC between 1 April 2017 and 31 March 2018 is listed in Annex 1.

2.2.2. Appointment of members

ISAC members are appointed 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 ISAC members are be found in Annex 2.

2.2.3. Declarations of interest

Members of 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 the removal of an individual from the Committee.

Members are also required 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

Over the reporting period, the Committee met four times in person on the following dates: 25 April 2017, 11 July 2017, 03 October 2017, and 29 January 2018. ISAC meetings were held at the MHRA offices located at 151 Buckingham Palace Road, Victoria, London SW1W 9SZ.

2.3.2. Member meeting expenses

During 2017/18 Committee members were entitled to claim a set £174 fee for preparation and attendance for each physical meeting. In addition, members were 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 was remunerated by the MHRA on a pro-rata basis for ISAC duties and did 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 as described in section 2.5. All phases of protocol review were overseen and signed-off by 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 any 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;
- The proposed study is relevant to public health
- 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.

During the course of some studies, it may become necessary to deviate from an ISAC approved protocol. Any small deviations from an approved protocol should be reported to the ISAC Secretariat, and significant deviations from an approved protocol, such as to the study design or analysis plan, require ISAC approval.

2.6. 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. The summary information on ISAC approved studies can be found at https://cprd.com/protocol-list.

2.7. Publication of ISAC approved studies

The findings of many studies approved by 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/.

2.8. Publication of ISAC activities

Summary minutes of ISAC meetings are published on both the CPRD and MHRA websites once the Committee has agreed the full minutes. The summary of ISAC minutes are available at https://cprd.com/ISAC-minutes-annual-reports.

The annual reports of 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://cprd.com/ISAC-minutes-annual-reports.

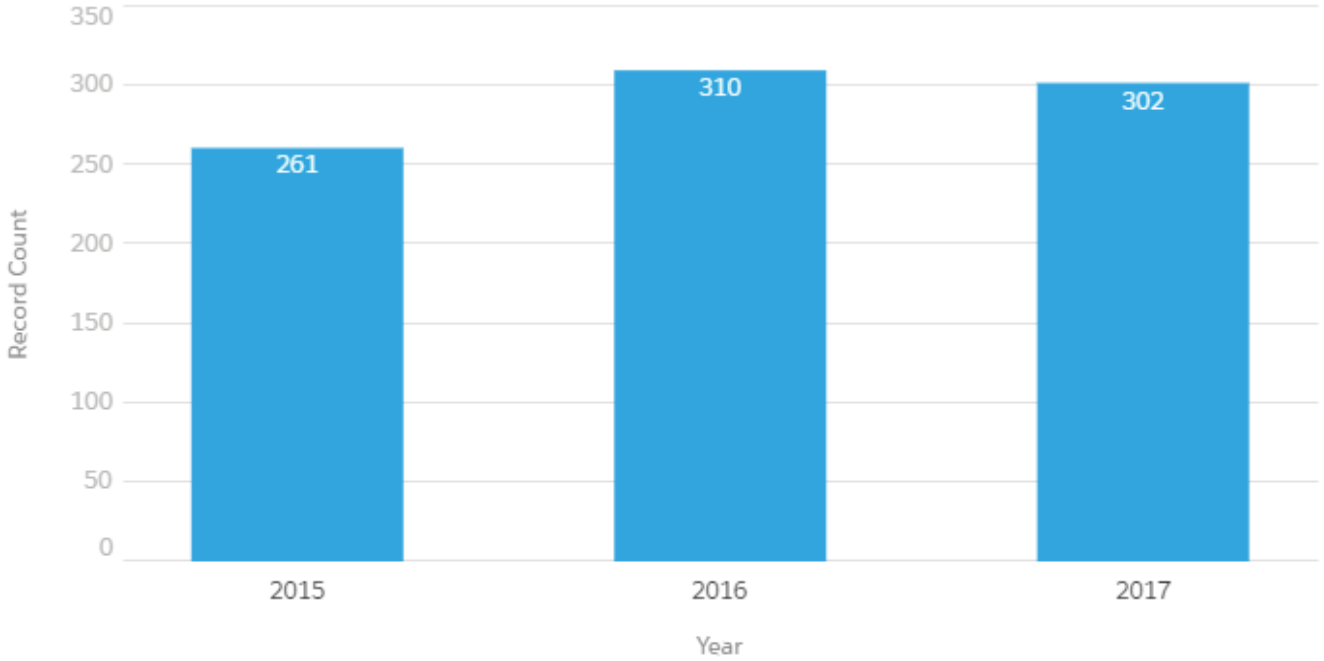
3. Activities and Outputs

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

During this reporting period, ISAC reviewed a combination of newly received research applications, as well protocol resubmissions and amendments from applications submitted in the current and previous reporting periods.

A total of 302 new research protocols requesting access to CPRD data were received in 2017/18, a 2.6% decrease on the previous financial year from 310[1] (Fig. 1[2]). The figure is obtained by counting protocols that have a submission received date within the given financial year.

Fig. 1 – New research applications received in financial years 2015/16, 2016/17, and 2017/18



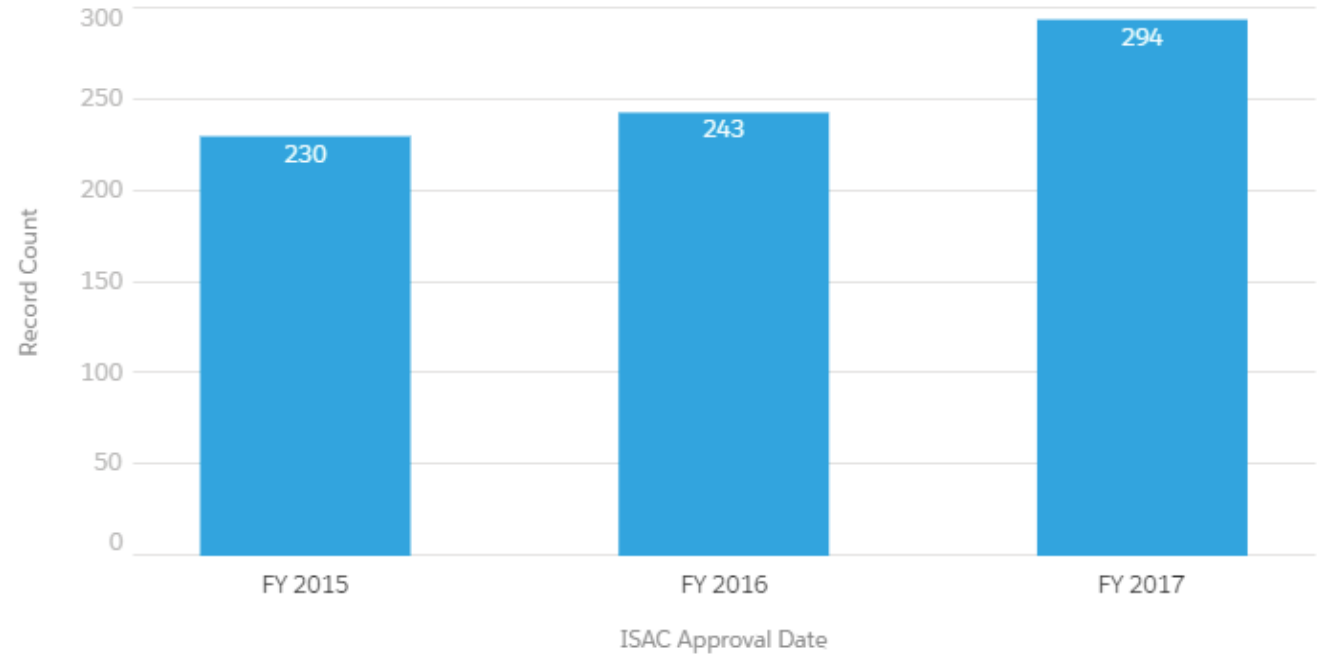
ISAC approved 294 applications in the reporting period, an increase of 21% on the previous financial year[3] (Fig. 2). The figures include protocols that have an ISAC approval date within the given financial year. Protocols approved in one financial year may have been submitted in a previous financial year, and therefore the figures differ from those for newly received applications listed above.

[1] The figure for received protocols stated in the ISAC Annual Report for 2016/17 was 309. This figure has since been corrected due to rectification of a classification error. References to year-on-year differences in this report are using the corrected figures.

[2] The ISAC Report published in 2016 covered a 15-month period from 01 January 2015 to 31 March 2016. The figures given in this report refer only to the 2015/16 financial year and may therefore differ from figures provided in the 15-month Committee Report.

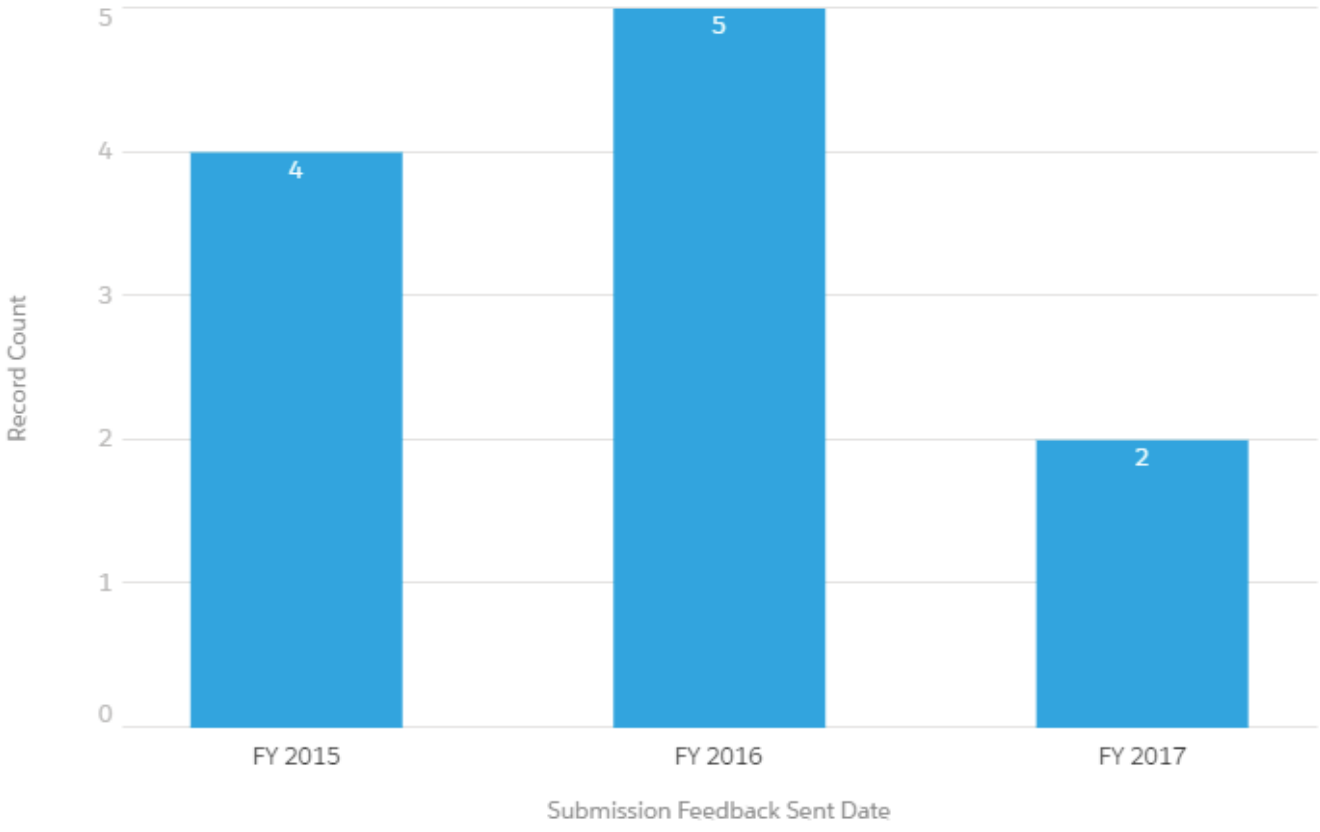
[3] The figure for approved protocols stated in the ISAC Annual Report for 2016/17 was 242. This figure has since been corrected due to rectification of a classification error. References to year-on-year differences in this report are using the corrected figures.

Fig. 2 – Research applications approved in financial years 2015/16, 2016/17, and 2017/18



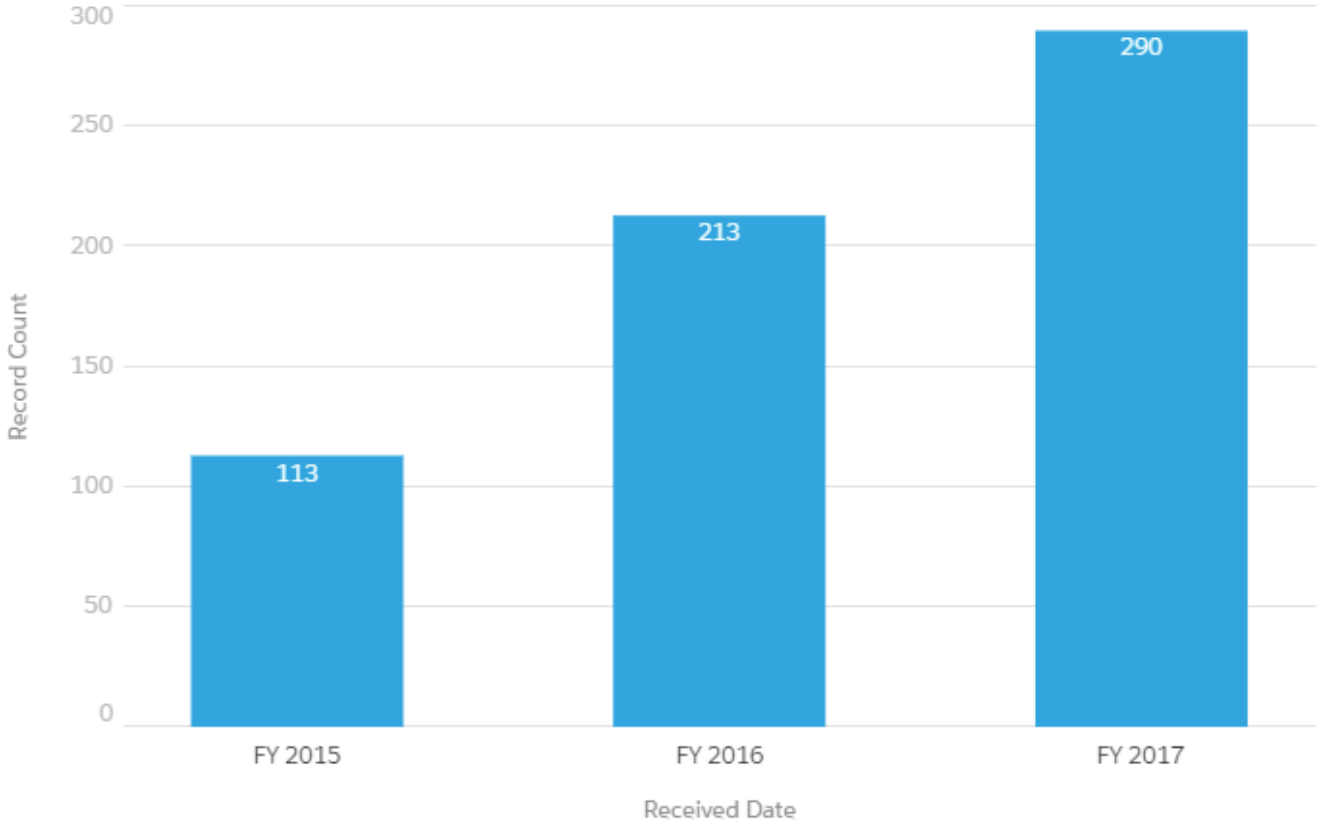
ISAC rejected 2 applications within the reporting period, a decrease of 60% on the previous year (Fig. 3).

Fig. 3 – Research applications rejected in financial years 2015/16, 2016/17, and 2017/18



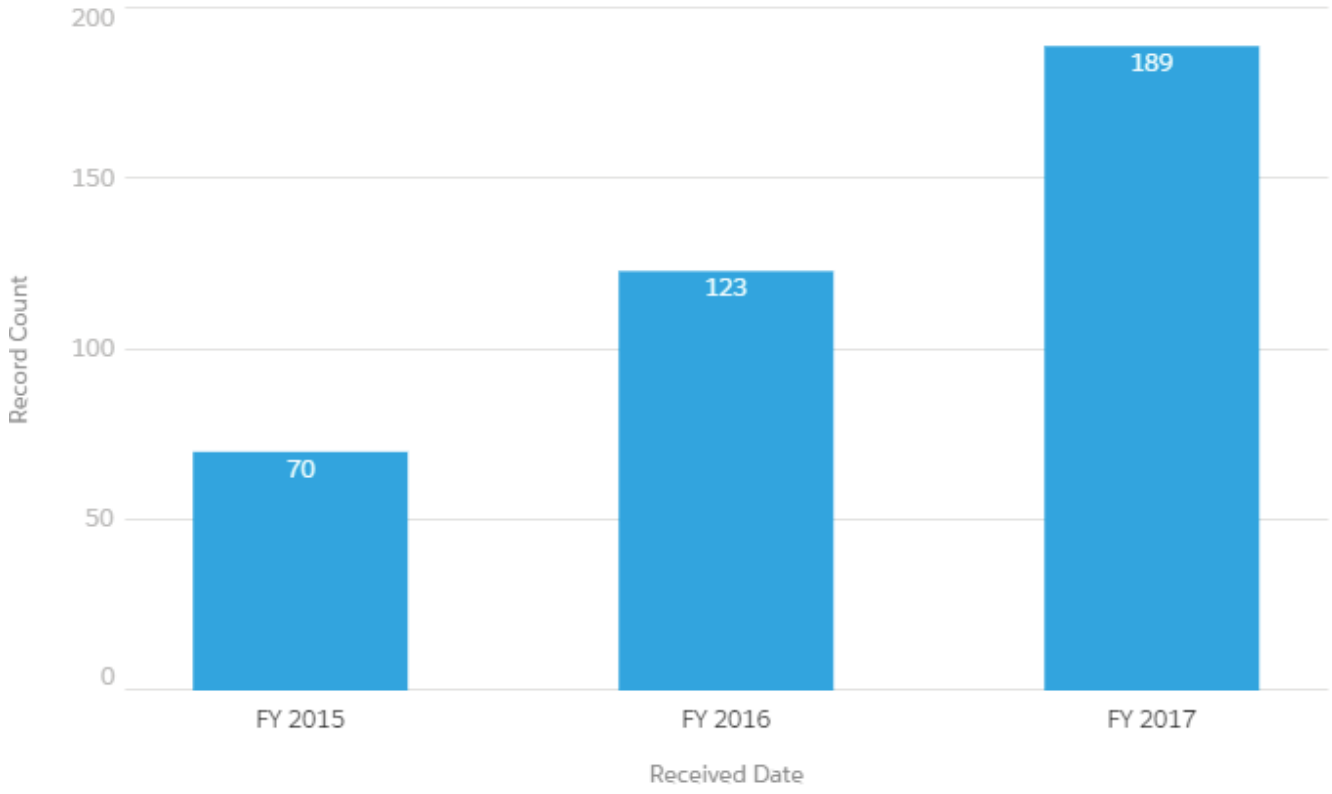
CPRD also received 290 resubmissions in the reporting period, an increase of 36% on the previous financial year (Fig 4). Resubmissions refer to resubmitted protocols that have previously been reviewed by ISAC and rated as 'Resubmission Required'. The figures are taken from resubmissions that are received within the given financial year and are independent from the date the protocol was first submitted to ISAC. It is possible that protocols initially submitted in one financial year may be resubmitted to ISAC in the next financial year.

Fig. 4 – Resubmissions received in financial years 2015/16, 2016/17, and 2017/18



The CPRD also received 189 amendments to previously approved protocols in the reporting period, a 54% increase on the previous financial year (Fig. 5). Amendments refer to requests submitted to ISAC to amend a previously approved protocol. The figures are calculated based on the financial year in which the amendment request was received and are independent from the date that the original protocol was submitted to or approved by ISAC.

Fig. 5 – Amendments received in financial years 2015/16, 2016/17, and 2017/18

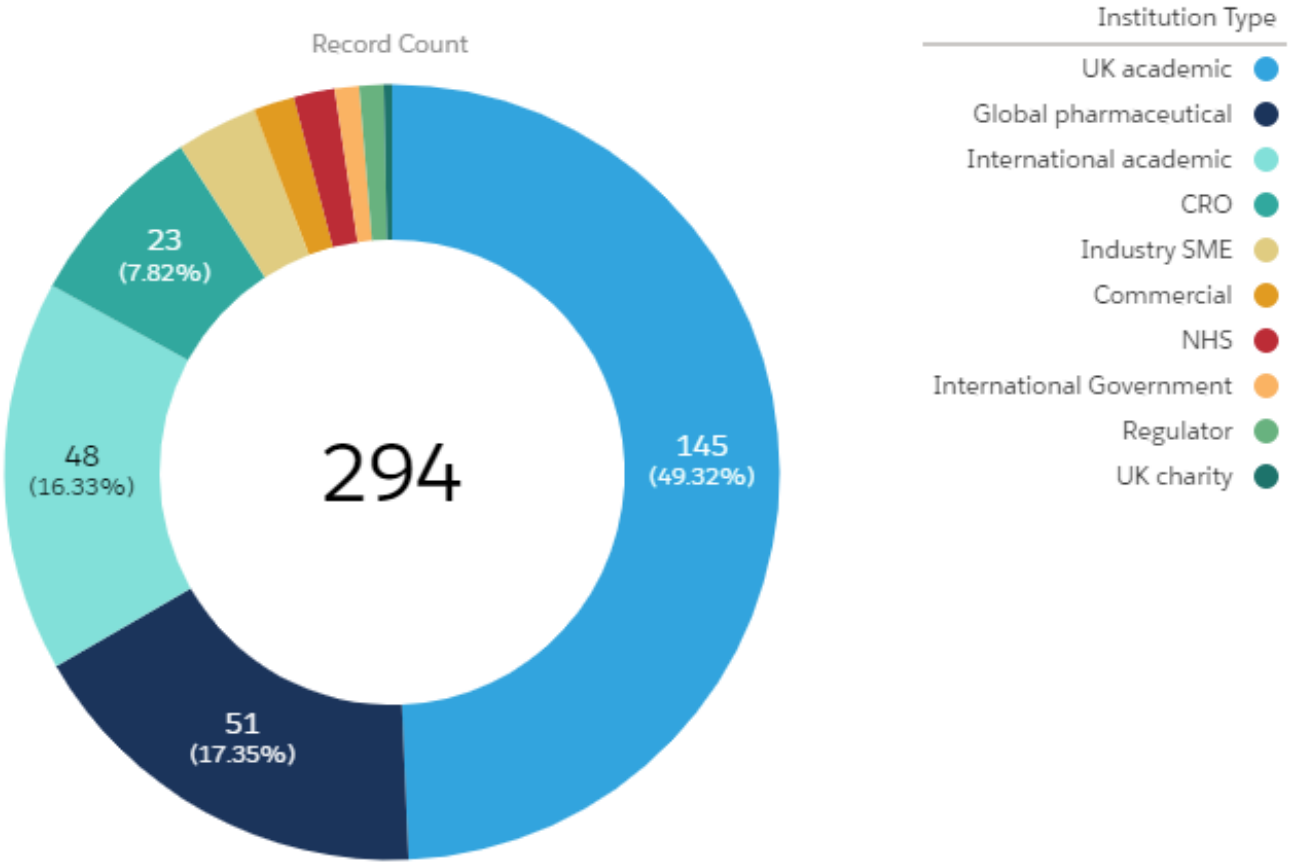


In total, ISAC made 773 decision during the reporting period; 299 decisions relating to protocols and 474 decisions relating to resubmissions and amendments – up from 579 in 2016/17 reporting year.[4] These figures are based on the date in which applicants were informed of the outcome of successfully submitted protocols, resubmissions and amendments falling within the 2016/17 and 2017/18 financial years.

[4] 293 decisions relating to protocols and 286 relating to resubmissions and amendments

Figure 6 presents a breakdown of the 294 protocols approved by ISAC in the reporting period, categorised by the Chief Investigator's organisational affiliation. The Chief Investigator can only be assigned a single organisational affiliation. The chart shows that nearly half of all approved protocols were led by researchers based in UK academic organisations.

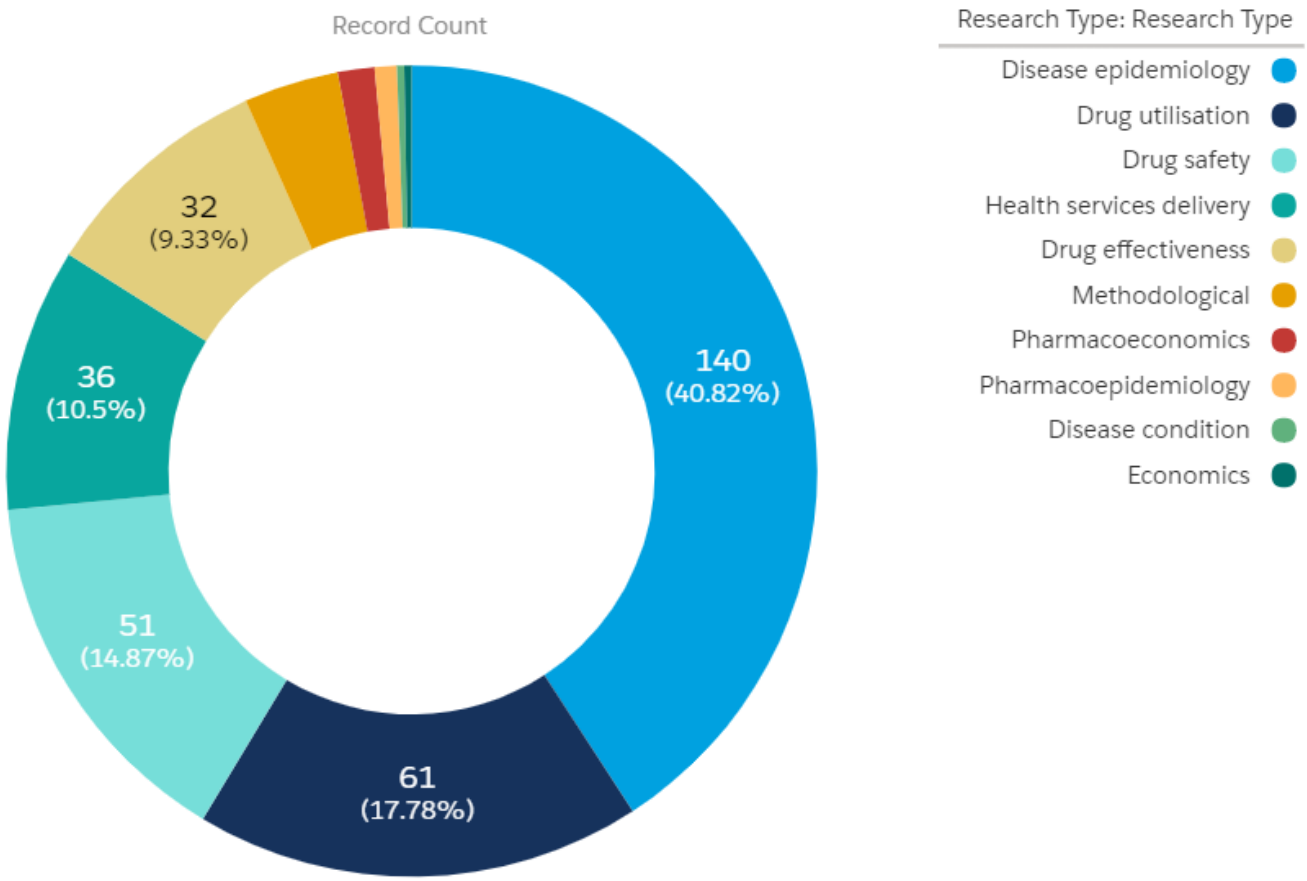
Fig. 6 – Number of approved protocols by Chief Investigator's organisational affiliation, 2017/18[5]



[5] Figures not shown: Industry SME, 10 (3.4%); NHS, 5 (1.7%); Commercial, 5 (1.7%); Regulator, 3 (1.02%); International Government, 3 (1.02%); UK Charity, 1 (0.34%).

Figure 7 provides an overview of the 294 approved protocols, categorised by research type. A protocol may be assigned to more than one study type by the applicant, for example, the figure shows that around 41% of protocols approved by ISAC listed 'disease epidemiology' as a research type.

Fig. 7 – Approved protocols by research type, 2017/18[6]



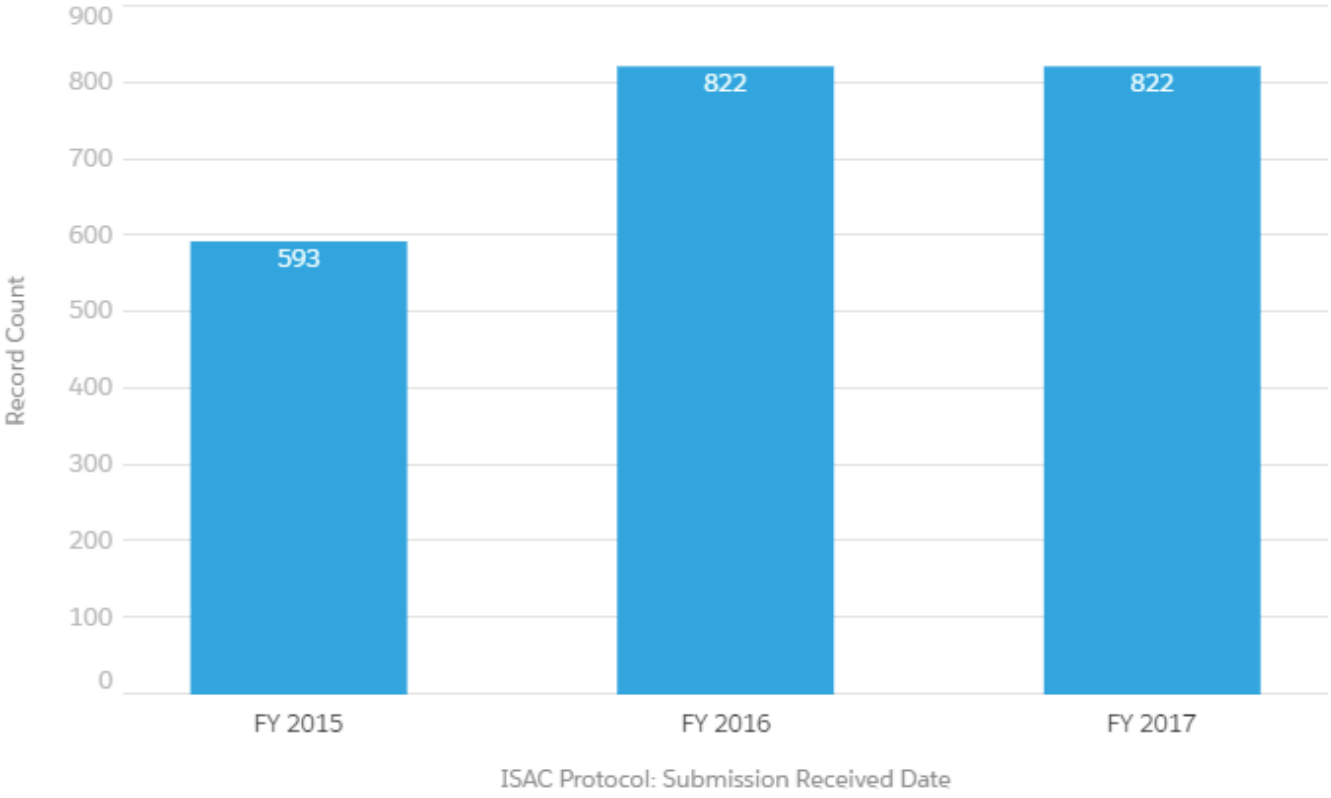
3.2. Protocol applications including requests for linkage to other datasets

The value of research using primary care data can be significantly augmented by linkage to other data sources. Primary care data collected by CPRD can be linked to a number of other patient level and area level datasets, including but not limited to: Hospital Episode Statistics, Office for National Statistics mortality data, National Cancer Registration and Analysis Service data, Mental Health Services Data Set, and Practice Level Index of Multiple Deprivation.

[6] Figures not shown: Methodological, 13 (3.79%); Pharmacoeconomics, 5 (1.46%); Pharmacoepidemiology, 3 (0.87%); Disease Condition, 1 (0.29%); Economics, 1 (0.29%). Applicants can select more than one research type per protocol.

A significant proportion of protocols submitted to ISAC request linkage to other data sets. Figure 8 shows that, from the 302 applications submitted to ISAC in the 2017/18 reporting period, there were 822 linked datasets being requested[7]. The data show that, on average, nearly three linkages are requested for each protocol submitted, and continues to highlight the importance of CPRD's data linkage service.

Fig. 8 – Linkages requested in ISAC applications submitted in financial years 2015/16, 2016/17, and 2017/18



3.3. ISAC update

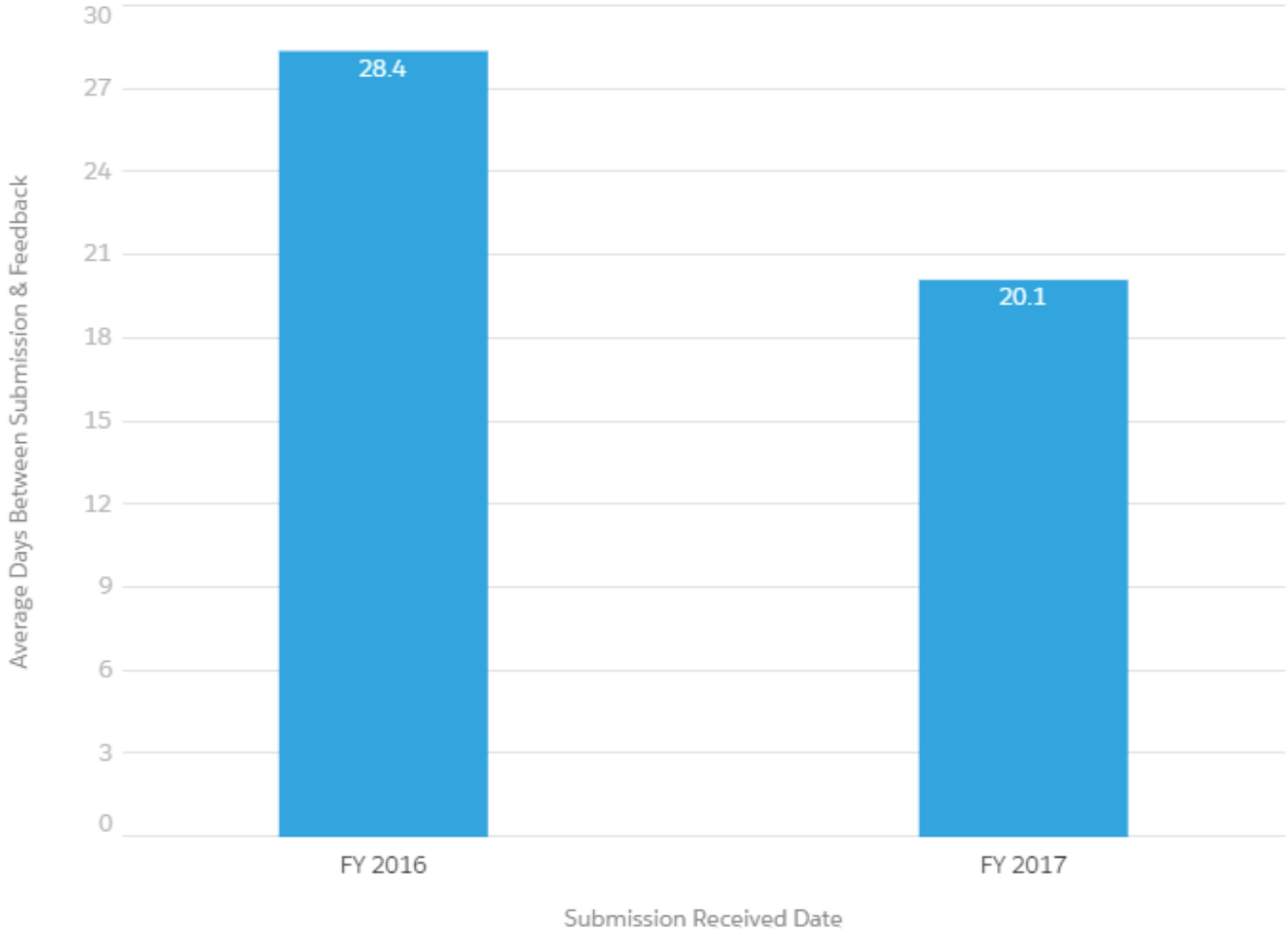
Over the course of the 2017/18 reporting year, a significant amount of work has been undertaken to digitise and automate parts of the ISAC review process. New Customer Relationship Management software is now able to report on data in real-time and allows for improved tracking of applications through the review process. This has had a positive impact on the time taken to review protocols.

ISAC aim to make a decision on submitted applications within 28 working days. This figure is taken to be the time between an application being successfully submitted to ISAC and the decision on that

[7] Figure correct at the time of publication. Linkages requested are categorised by the financial year in which the original protocol was submitted to ISAC. Amendments received in subsequent reporting periods will cause these figures to change slightly.

protocol being communicated to the applicant. Figure 9 shows that the average time taken to make a decision on submitted applications in 2017/18 was just over 20 working days. Notably, this figure is 29% lower than the average time for the 2016/17 reporting period, despite a 34% increase in workload for ISAC.[8]

Fig. 9 – Average working days between protocol submission and feedback sent date in financial years 2016/17 and 2017/18



3.4. Summary

In summary, although the number of new ISAC applications received in the reporting period was at a similar level to the 2016/17 financial year, the workload for ISAC increased 34%. This is largely due to 36% and 54% increase respectively, in resubmissions and amendments submitted to ISAC in 2017/18 compared to the previous financial year.

[8] Taken to be the total number of ISAC decisions that fall within the given financial year, which were reported above as 579 and 773 in 2016/17 and 2017/18 respectively.

Of the 294 protocols approved in the reporting period, nearly 50% were led by UK academic institutions, and over 40% were categorised as disease epidemiology research, which are broadly the same as reported in the previous financial year.

Data linkage remains an important CPRD service, with 244 of the 294 protocols approved in the reporting period requesting linkage to one or more other data sources.[9]

[9] Figure correct at time of publication

Annex 1 – Membership over 2017/18 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

Dr Iain Carey (Appointed 13 November 2017)
Senior Lecturer in Epidemiology, St George's, University of London

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 David Fishwick MBChB FRCP (Glasgow and London) AFOM MD (Appointed 13 November 2017

Honorary Professor of Occupational and Environmental Respiratory Disease, University of Sheffield

Dr Kate Fleming MA Cantab MSc PhD PGCHE (Appointed 01 January 2018)

Senior Lecturer in Social Epidemiology, University of Liverpool

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

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

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 & Departmental Lecturer – Nuffield Department of Primary Care Health Sciences, University of Oxford

Professor Andrew Morris BSc MSc PhD (Appointed 15 December 2017)

Chair in Statistical Genetics. Institute of Translational Medicine, University of Liverpool

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 Grace Okoli PhD, MBChB, MRCGP (Appointed 13 November 2017)

Clinical Lecturer, School of Population Health and Environmental Sciences Faculty of Life Sciences and Medicine, King's College London

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

Professor Martin Tobin (Appointed 15 December 2017)
Director of Leicester Precision Medicine Institute and Professor of Genetic Epidemiology and Public Health, University of Leicester

Dr Hester Ward (Appointed 1 January 2016)
Consultant in Public Health Medicine (Health Informatics)

Dr Paul Welsh (Appointed 13 November 2017)
Senior Lecturer, Institute of Cardiovascular and Medical Sciences, University of Glasgow

Dr Stephen Weng (Appointed 13 November 2017)
NIHR Research Fellow, Division of Primary Care, Faculty of Medicine & Health Sciences, University of Nottingham

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 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 Early Years in the Administrative Data Research Partnership, PI on Growing up in Wales program. She is also Deputy Director in the Centre for the Development and Evaluation of Complex Interventions for Public Health Improvement a reviewer for the Health Research Board for Ireland and training lead in HDRUK Wales, as well as being the Associate Editor in BMC Public Health and previously the Pharmacoepidemiology lead (CIPHER –Centre for the Improvement of Population Health through E-records Research) within the FARR Institute and Co-Director of the Welsh Arthritis Research Network. She also has expertise in developing electronic cohort studies.

Dr Iain Carey is Senior Lecturer in Epidemiology at St George's, University of London. He has been involved in research projects utilising primary care databases since 2001, including DIN, THIN and CPRD. His research interests have focused on issues pertinent to older people, such as polypharmacy and inappropriate prescribing, the quality of care in elderly care homes and the impact of bereavement in the elderly.

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 worked at the University of Bristol since 2007 - in the Department of Population Health Sciences, Bristol Medical School. 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. 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 David Fishwick is currently a Consultant Respiratory Physician with a major clinical and research interest in occupational lung disease, holding the following roles; Consultant Respiratory Physician, STH Foundation NHS Trust, Co-Director of the Centre for Workplace Health (CWH), and the Chief Medical Adviser of the Health and Safety Executive of Great Britain. In addition, he is an Honorary Professor of Occupational and Environmental Respiratory Medicine, University of Sheffield, awarded in 2010.

Dr Kate Fleming is a Senior Lecturer in Social Epidemiology at the University of Liverpool. Her research focuses on the epidemiology of alcohol use, of pregnancy and child health, and on the use of linked electronic health records for epidemiological research. At the intersection of this she is particularly interested in how we might measure the harms caused by alcohol exposure in pregnancy. Following a primary degree in Natural Sciences (Pharmacology) from University of Cambridge and an MSc in Epidemiology from LSHTM, Kate previously worked at the University of Nottingham focussing on studies using the CPRD, including her own PhD on liver disease.
In addition to her research activity, Kate has substantial commitments to the teaching of public health for the undergraduate MBChB programme at the University of Liverpool.

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 of 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.

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.

Professor 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.

Ms 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 and Departmental Lecturer in the Nuffield Department of Primary Care Health Sciences at the University of Oxford, and a member of the Centre for Evidence Based Medicine. Her research interests include the use of large routine databases in medical research and research design. As part of the postgraduate Evidence Based Health Care programme, she coordinates the Big Data Epidemiology module and lectures in Study Design and Research Methods. 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 Andrew Morris is Chair of Statistical Genetics at the University of Liverpool, and Visiting Professor at the Estonian Genome Centre and the University of Oxford. He obtained a BSc in Statistics (1994) and an MSc in Biometry (1995), before undertaking a PhD in Statistical Genetics. He has worked as part of major international collaborations, including the International HapMap Consortium and the Wellcome Trust Case Control Consortium, and was awarded a Wellcome Trust Senior Research Fellowship in 2007. Andrew moved to the University of Liverpool in 2014 to take up the newly-established Chair of Statistical Genetics. His research has focused on the development of methodology for the analysis of genome-wide association and re-sequencing studies, recently considering rare variants and trans-ethnic analyses, and complex clinical outcomes in pharmacogenetics. He is currently a leading analyst in international collaborative efforts to understand the genetic basis of a wide range of complex human traits and diseases, including type 2 diabetes, kidney function, blood pressure, anthropometric measures and endometriosis.

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. 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.

Dr Grace Okoli is a general practitioner who lives and works in south London. She works as a clinical lecturer in the department on a part-time basis. With a background in molecular and cellular biology, she completed her PhD at Imperial College London. On completion of her doctorate, she became a post-doctoral researcher at Johns Hopkins School of Medicine in the United States, where she worked on developing an oral gene delivery system for the management of haemophilia – the protocol is currently under patent. At present, she is interested in the use of biomarkers in primary care to aid the early diagnosis of disease. In addition, Grace is a public governor for King's College Hospital, where her primary goal is to improve the working relationship between the hospital and its partners in primary care.

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, University of London. 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.

Ms 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.

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.

Professor Martin Tobin is a Fellow of the Academy of Medical Sciences, Professor of Genetic Epidemiology and Public Health at the University of Leicester, and Chair of the Leicester Precision Medicine Institute. He leads a programme of research on the genomics of common, complex diseases and traits with particular emphasis on the genetics of lung health and COPD. He leads one of the major clinical partnerships for Genomics England (Quantitative Methods, Machine Learning and Functional Genomics), the SpiroMeta consortium, and the EXCEED study. Key interests including early career research training, public engagement and genomic-driven precision medicine in non-European ancestries. He contributes to panels and advisory committees for the Medical Research Council and the Academy of Medical Sciences.

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.

Dr Paul Welsh is a senior lecturer at University of Glasgow. Following completion of his PhD in 2008, he obtained two separate British Heart Foundation Fellowships and completed an MSc in Epidemiology at London School of Hygiene and Tropical Medicine (Distinction, 150th Anniversary Prize). He has a wide range of research interests including the epidemiology of cardiovascular disease, diabetes, and inflammatory diseases, and he has a specific interest in biomarkers of disease.

Dr Stephen Weng is an Assistant Professor of Integrated Epidemiology and Data Science who leads the data science research within the Primary Care Stratified Medicine Research Group. Dr Weng integrates traditional epidemiological methods and study design with new informatics-based approaches, harnessing and interrogating "big health care data" from electronic medical records for the purpose of risk prediction modelling, phenotyping chronic diseases, data science methods research, and translation of stratified medicine into primary care.

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 (2017/18)

	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 (Deputy Chair)	Novartis	Member of Data Monitoring 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	
Dr Iain Carey	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	No
Prof David Fishwick	None	N/A	None	N/A	
Dr Kate Fleming	None	N/A	None	N/A	No

	Personal Interests		Non-Personal Interests		Current Interest
Member	**Name of Company**	**Nature of Interest**	**Name of Company**	**Nature of Interest**	
Prof Peter Helms	None	N/A	None	N/A	
Dr Caroline Jackson	None	N/A	None	N/A	
Dr Wendy Knibb	None	N/A	None	N/A	
Prof Evangelos Kontopantelis	None	N/A	None	N/A	
Ms 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 Andrew Morris	None	N/A	None	N/A	No
Prof Keith Neal	None	N/A	None	N/A	
Dr Grace Okoli					
Dr Jennifer Quint	AstraZeneca	Consultancy	AstraZeneca	Grants	Yes
	GlaxoSmithKline	Consultancy	GlaxoSmithKline	Grants	Yes
	Bayer	Consultancy	Bayer	Grants	Yes
	Insmed	Consultancy	Insmed	Grants	Yes
	Boehringer Ingelheim	Consultancy	Boehringer Ingelheim	Consultancy	Yes
			IQVIA	Consultancy	Yes
Ms Marcia Saunders	None	N/A	None	N/A	
Prof Sara Thomas	None	N/A	None	N/A	
Prof Martin Tobin	None	N/A	GSK	BBSRC CASE studentship to Alex	Yes

	Personal Interests		Non-Personal Interests		Current Interest
Member	**Name of Company**	**Nature of Interest**	**Name of Company**	**Nature of Interest**	
				Williams (joint supervisor with GSK) Respiratory Genomic Collaboration with University of Leicester (co-investigator)	
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
Dr Paul Welsh	None	N/A	Boehringer Ingelheim	Grant	Yes
			Roche	Contract/grant for cohort phenotyping	Yes
Dr Stephen Weng	Road to Health Ltd.	Consultancy			Yes
			Amgen	Grant	Yes
Prof Ian Wong	Therakind	Director and shareholder			Yes
	Healthcare Innovation Technology Service (UK)	Director			Yes
	Jacobson Pharmaceutical (Hong Kong)	Consultancy			Yes