Medicines & Healthcare products Regulatory Agency

CPRD

Independent Scientific Advisory Committee (ISAC)

Annual Report

1 April 2018 to 31 March 2019

NHS National Institute for Health Research

Produced by the MHRA

Contents

Glossary

CAG	Confidentiality Advisory Group
CPRD	Clinical Practice Research Datalink
CPRD Aurum	One of CPRD's primary care data collection databases
CPRD GOLD	GP On-Line Database (one of CPRD's primary care data collection database)
EHR	Electronic Health Record
EMIS Health®	GP system software provider
GP	General Practitioner
HRA	Health Research Authority
HSCIC	Health & Social Care Information Centre (operating as NHS Digital since 2016)
IG	Information Governance
ISAC	Independent Scientific Advisory Committee
MHRA	Medicines and Healthcare products Regulatory Agency ("the Agency")
N3	The high-speed broadband network for the NHS
NDG	National Data Guardian
NHS	National Health Service
NIHR	National Institute for Health Research
REC	Research Ethics Committee
Vision®	GP system software provider

Foreword from the Chairman of the MHRA

It is a pleasure to present the 2018/19 Annual Report of the MHRA Independent Scientific Advisory Committee (ISAC). This year marks the 30th anniversary of the Clinical Practice Research Datalink (CPRD). From its humble beginnings when a group of GP practices first shared their medical records to better understand patient health, CPRD has grown into the most widely used population health data resource globally. Within the MHRA, CPRD data are used every day as an essential component of medicines safety and surveillance activities. Research using CPRD data has resulted in 2200 peer-reviewed publication and informed a plethora of drug safety guidance and clinical guidelines. These outputs are a testament to the growing numbers of GPs who understand the importance of securely sharing their anonymised patient data to support evidence-based medicine, leading to better patient and public health outcomes. Today, 30 years from CPRD's inception, 1400 GP practices across the UK, representing 1 in every 7 GP practices, contribute data to CPRD. Such endorsement of the importance of research from a busy GP community is truly remarkable. We remain indebted to these GPs, without whom we couldn't reliability evaluate the safety of medicines, risks to public health and best approaches to delivering healthcare.

I would like to pay tribute to the time and expertise of the members of ISAC in their vital role reviewing research applications to use CPRD primary care and linked data. Under the expert stewardship of the ISAC Chair, Professor Deborah Saltman AM, ISAC members have not only reviewed a high volume of research applications this year, but they have reduced the timeframe for feeding back decisions to applicants. The MHRA is most grateful to the Chair and all members of the ISAC for the sterling work they have done to ensure research using CPRD data benefits public health and is conducted in a robust manner. Research approved by ISAC is published on the CPRD website. Reading these summary protocols unequivocally demonstrates the value of responsibly sharing anonymised health records for public and patient gain. Building on the significant contribution to drug safety and public health over the past three decades, we look forward to new insights arising from research using CPRD data over the next 30 years.

Professor Sir Michael Rawlins GBE Kt MD FRCP
Chair MHRA Board

Foreword from the Chair of ISAC

This is the fourth foreword to the Committee's Annual Report that I have written since I was appointed as Chair of ISAC in February 2016, and 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 similar number of new research protocols received compared to the previous reporting period, however the number of approvals has increased by 23%, and the number of resubmissions has decreased by 16%. Once again, the number of amendments received has increased by 57% compared to last year. Once again, the Committee has further reduced the average time for feedback on applications, with feedback now provided in just over 16 days from submission on average. 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 continues to highlight 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; Professor Ann John, Dr Wendy Knibb, Ms Sally Malin, Ms Marcia Saunders, Professor Sonia Saxena, and Professor Sara Thomas. The important contributions by these members has been invaluable for ensuring research conducted using CPRD data is of a high standard and will benefit patient and public health. The success of the ISAC is dependent on the voluntary contributions offered by members and I would like to thank them for their continuing contributions to the 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, 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 2019/20.

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 and Social Care. 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 (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 1 April 2018 to 31 March 2019.

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. CPRD data are used worldwide by regulators, academic researchers and the life science industry for observational and interventional public health and clinical studies. Over 2,200 peer-reviewed articles using CPRD data have been published to date. Recent studies have contributed to the development of best practice and clinical guidelines, such as demonstrating the safety and protective effect of the meningococcal vaccine in infants, and covered important issues such as adolescent mental health and the care needs of people with multiple health conditions

CPRD data are sourced from a UK-wide network of 1,400 GP practices across the UK. The CPRD database contains anonymised primary care electronic health records (EHR) on more than 35 million patients, of which 11 million are currently registered at contributing GP practices. EHR in the CPRD database have a median follow-up of 10 years, with 25% of the data having 20 years follow-up.

The CPRD database contains coded data from anonymised primary care EHR 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 has Research Ethics Committee (REC) approval 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 (CAG), for contributing GP practices to supply patient identifiers to NHS Digital, allowing CPRD to supply anonymised linked data for public health research. [CAG reference number: ECC5-05(a)/2012]

As an organisation that has access to de-identified patient data, CPRD also completes an annual online self-assessment tool called Data Security and Protection Toolkit. This allows CPRD to measure itself against the 10 National Data Guardian (NDG) data security standards.

CPRD operates a GP opt-in model, whereby a GP practice agrees to contribute their anonymised patient records to CPRD. GPs are provided with Fair Processing Notices to inform patients of the facility to opt-out of their data being shared with CPRD for research purposes. CPRD does not collect EHR of patients who have opted out of sharing their data for research.

1.2.3. Data collection

CPRD manages the collection of data from GP practices that either 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 comprises 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 is not known to 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 assigned 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 provides a linkage service for CPRD enabling data from participating English GP practices to be linked to other health-related data sources while upholding patient confidentiality.

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

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 has both 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 19 members, including the Chair. 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 ISAC). Membership of ISAC between 1 April 2018 and 31 March 2019 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 can 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 twice in person on the following dates: 9 April 2018, and 23 October 2018. ISAC meetings were held at the MHRA offices located at 151 Buckingham Palace Road, Victoria, London SW1W 9SZ and, from July 2018, 10 South Colonnade, Canary Wharf, London E14 4PU.

2.3.2. Member meeting expenses

During 2018/19 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 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 all CPRD research protocol submissions was performed virtually 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 the ISAC Chair.

2.4. Secretariat

The ISAC Secretariat, consisting of MHRA 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 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

Summary information about each ISAC-approved research protocol is published 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.

2.9. Other ISAC activities

The ISAC Deputy Chair, Professor Richard Stevens, presented findings and lessons learned from an audit exercise undertaken by ISAC of papers using CPRD data that were published in 2013 at the CPRD Mid-year User Group held on the 10 May 2018. The aim of Professor Stevens' presentation was to explain the original purpose of the exercise and provide an opportunity to gather feedback from researchers on how a future audit could add value. Slides from this presentation can be found in Annex 4. The key objective of the audit exercise was to compare the objectives, design and analyses between the protocol and publication to identify and assess the extent of major deviations from ISAC approved protocols. There were a number of positive outcomes from the audit including:

- ISAC guidance on major and minor amendments has been clarified;
- CPRD data licence terms place an obligation on researchers to specify the approved ISAC protocol number in the resulting publication to enable cross-referencing for future audits;
- CPRD publishes summaries of all approved ISAC protocols submitted to CPRD from 1 July 2015 on its website as part of its transparency policy (https://www.cprd.com/protocol-list);
- CPRD conducts a monthly online search of publications using CPRD data and maintains a bibliography of such publications on its website (https://www.cprd.com/bibliography);
- The CPRD Research team monitors publications based on CPRD data on a quarterly basis to ensure that any work conducted is within the scope of the data access terms and conditions.

ISAC members were engaged as part of the discovery phase of CPRD's planned electronic research applications portal (eRAP) project. The aim of the eRAP project is to develop an online application portal which will replace the current email-based method of submitting protocols to CPRD. Feedback from the Committee will inform the development of the portal.

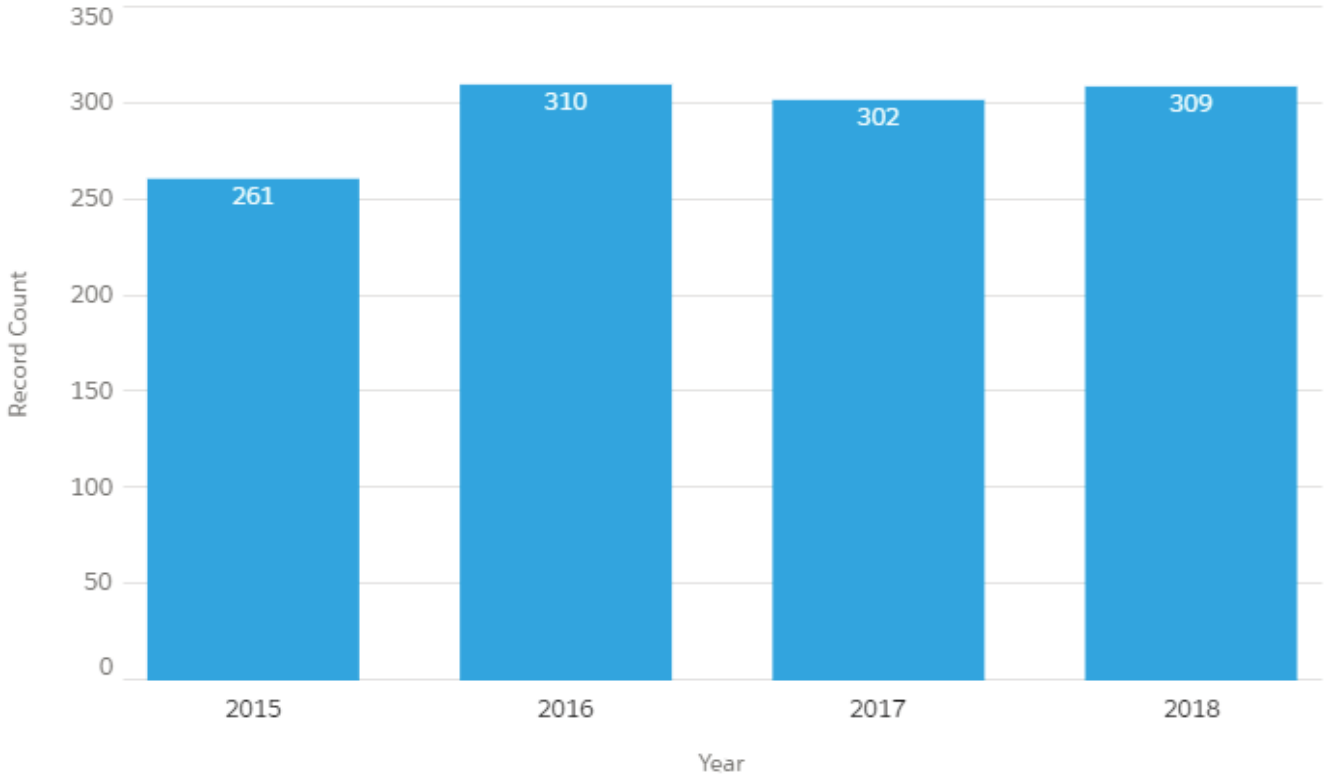
3. Activities and Outputs

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 as protocol resubmissions and amendments from applications submitted in the current and previous reporting periods.

A total of 309 new research protocols requesting access to CPRD data were received in 2018/19, a 2.3% increase on the previous financial year from 302 (Fig. 1)[1]. The figure is obtained by counting protocols that have a 'submission received' date within the given financial year.

Fig. 1 – New research applications received between financial years 2015/16 and 2018/19



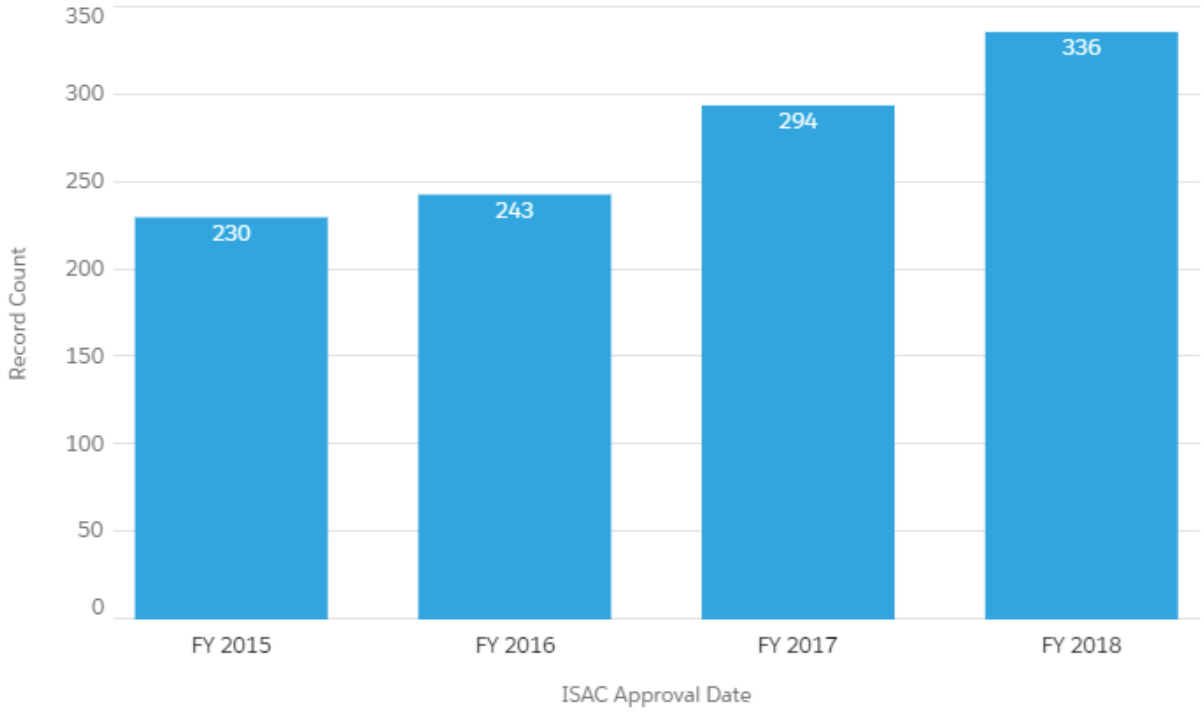
ISAC approved 336 applications in the reporting period, an increase of 14% on the previous financial year[2] (Fig. 2). The figures include protocols that have an ISAC approval date within the given financial

[1] The ISAC Report published in 2016 covered a 15-month period from 1 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.

[2] 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.

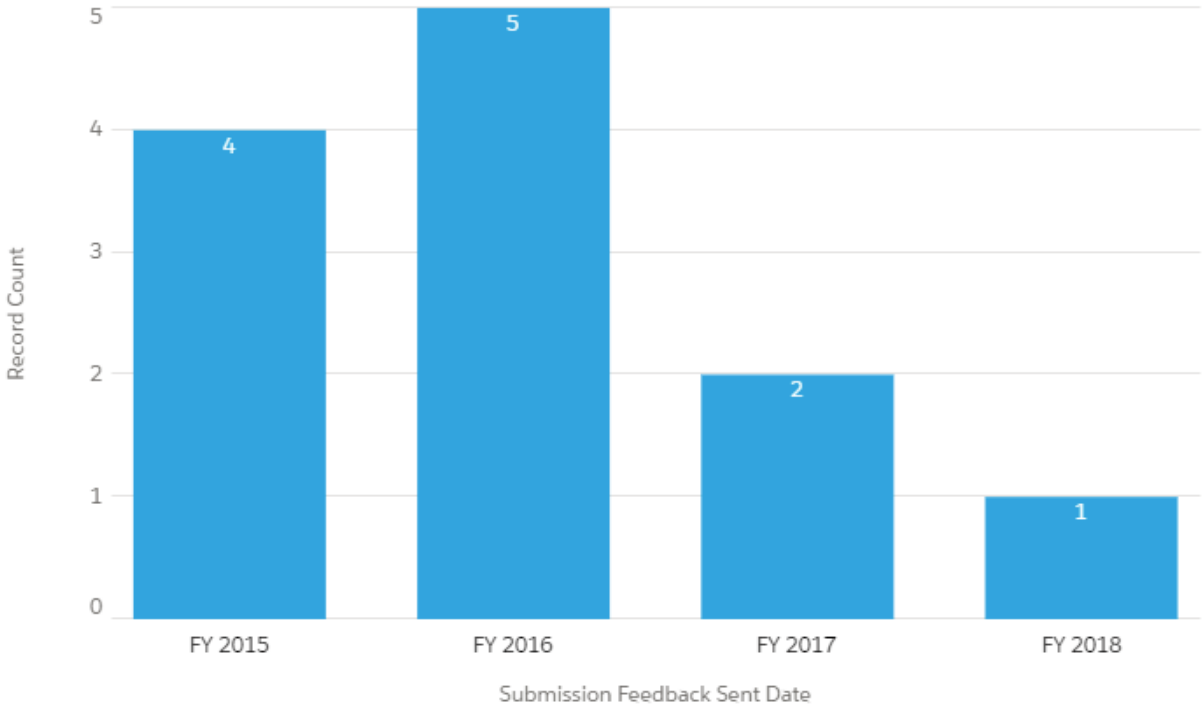
year. Protocols approved in one financial year may have been submitted in a previous financial year, and therefore the figures differ from those for newly received applications listed above.

Fig. 2 – Research applications approved between financial years 2015/16 and 2018/19



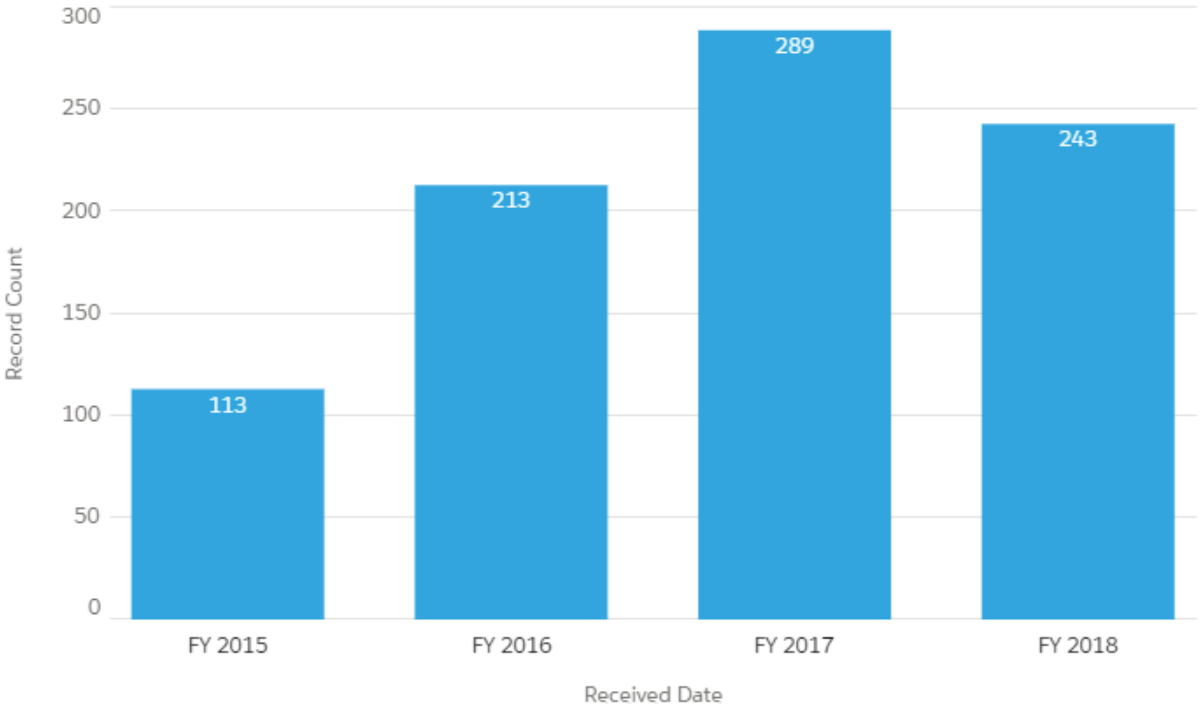
ISAC rejected 1 application within the reporting period (Fig. 3).

Fig. 3 – Research applications rejected between financial years 2015/16 and 2018/19



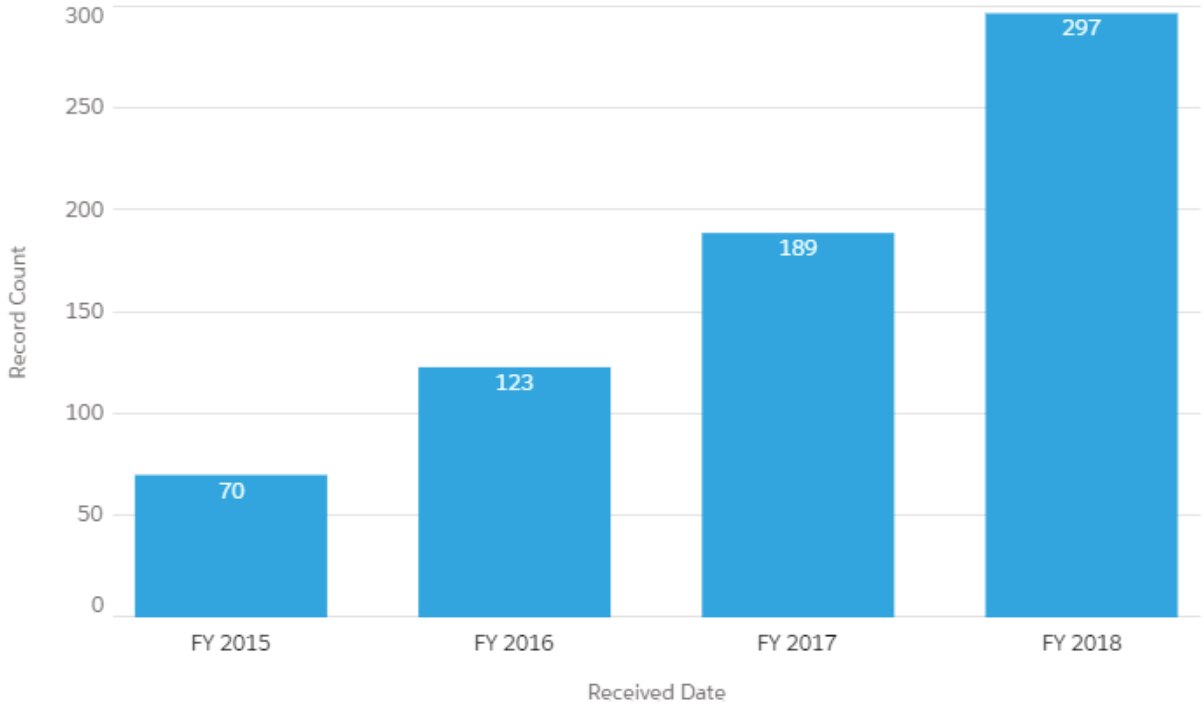
CPRD also received 243 resubmissions in the reporting period, a decrease of 16% on the previous financial year (Fig 4). Resubmissions refer to resubmitted protocols that have previously been reviewed by ISAC and rated as 'Resubmission Required'. The figures are taken from resubmissions that are received 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 between financial years 2015/16 and 2018/19



CPRD also received 297 amendments to previously approved protocols in the reporting period, a 57% 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 of the date that the original protocol was submitted to or approved by ISAC.

Fig. 5 – Amendments received between financial years 2015/16 and 2018/19



In total, ISAC made 685 decisions during the reporting period; 307 decisions relating to protocols and 378 decisions relating to resubmissions and amendments – down from 761 in 2017/18 reporting year.[3] These figures are based on the financial year in which applicants were informed of the outcome of successfully submitted protocols, resubmissions and amendments rather than the date of submission.

Figure 6 presents a breakdown of the 336 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.

[3] The 2017/18 ISAC Annual Report stated this figure incorrectly as 773. This was due to 12 protocol resubmissions/amendments being included that had failed validation and therefore should not have been categorised as 'successfully submitted'.

Fig. 6 – Number of approved protocols by Chief Investigator's organisational affiliation, 2018/19[4]

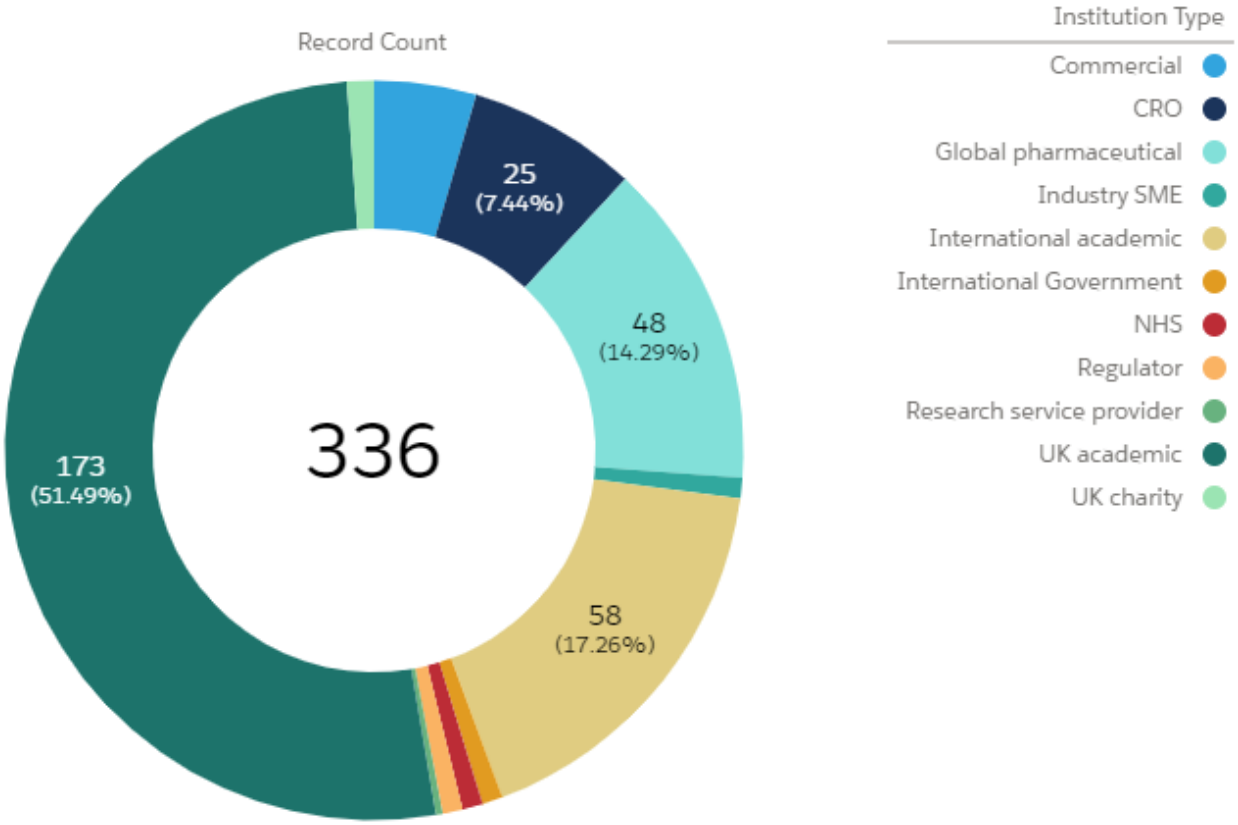
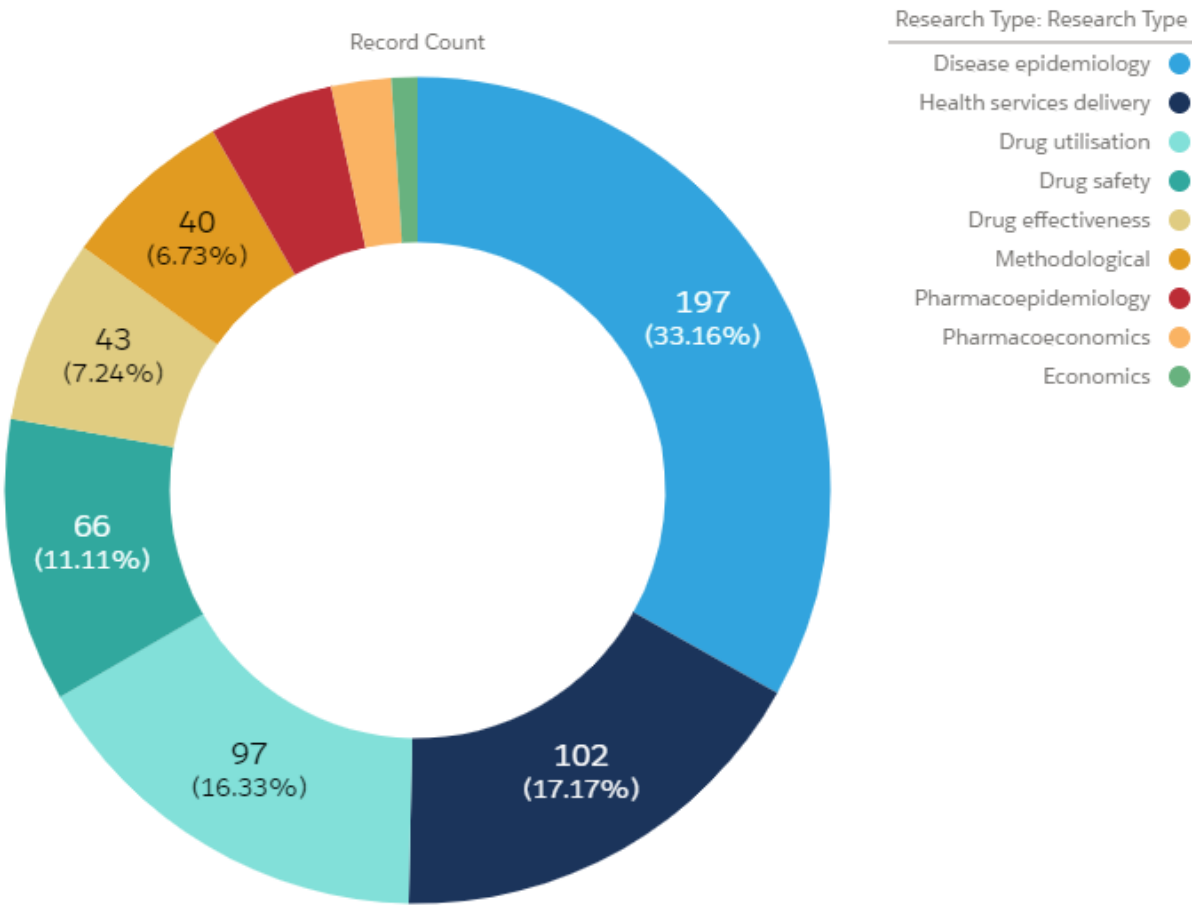


Figure 7 provides an overview of the 336 approved protocols, categorised by research type. A protocol may be assigned to more than one study type by the applicant. The Figure shows that most applicants describe their research as being disease epidemiology.

[4] Figures not shown: Commercial, 15 (4.46%); UK Charity, 4 (1.19%); Industry SME, 3 (0.89%); NHS, 3 (0.89%); Regulator, 3 (0.89%); International Government, 3 (0.89%); Research Service Provider, 1 (0.3%).

Fig. 7 – Approved protocols by research type, 2018/19[5]



3.2. Protocol applications including requests for linkage to other datasets

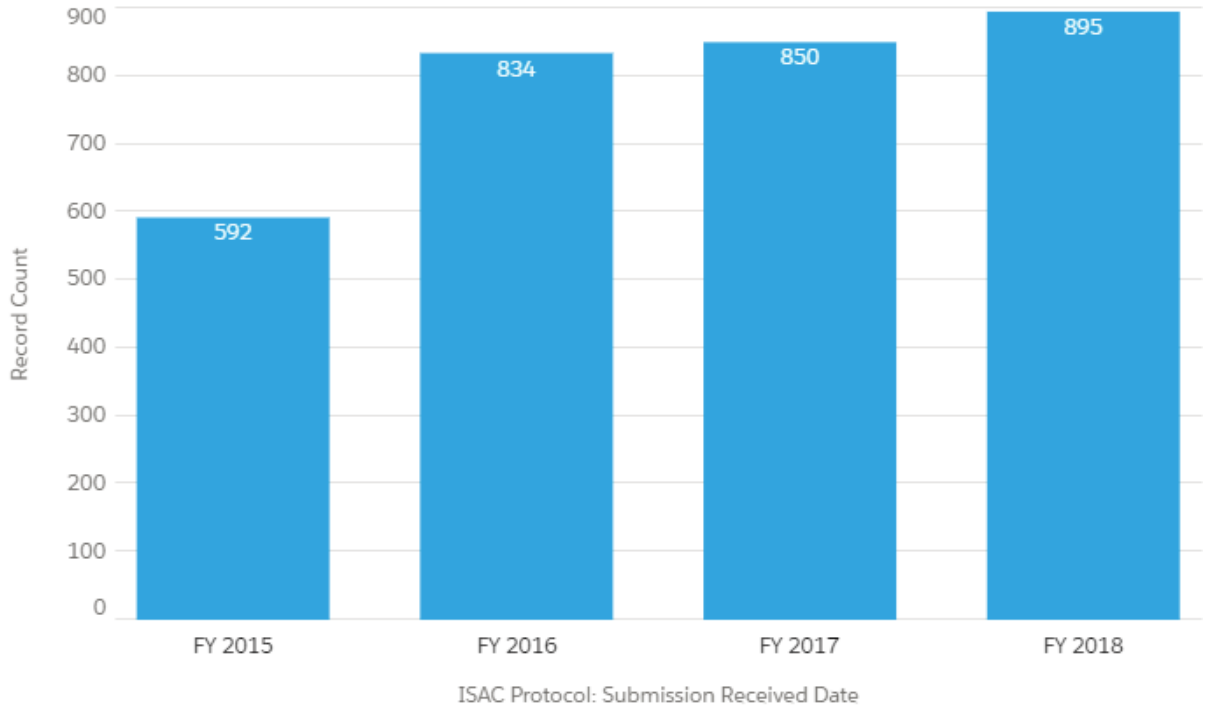
The value of research using primary care data can be significantly augmented by linkage to other data sources. Primary care data collected by CPRD can be linked to a number of other patient level and area level datasets, including but not limited to: Hospital Episode Statistics, Office for National Statistics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

A significant proportion of protocols submitted to ISAC request linkage to other data sets. Figure 8 shows that, from the 309 applications submitted to ISAC in the 2018/19 reporting period, there were 895 linked datasets being requested[6]. 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.

[5] Figures not shown: Pharmacoepidemiology, 29 (4.88%); Pharmacoeconomics, 14 (2.36%); Economics, 6 (1.01%). Applicants can select more than one research type per protocol.

[6] Figures correct at the time of writing. 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.

Fig. 8 – Linkages requested in ISAC applications submitted between financial years 2015/16 and 2018/19

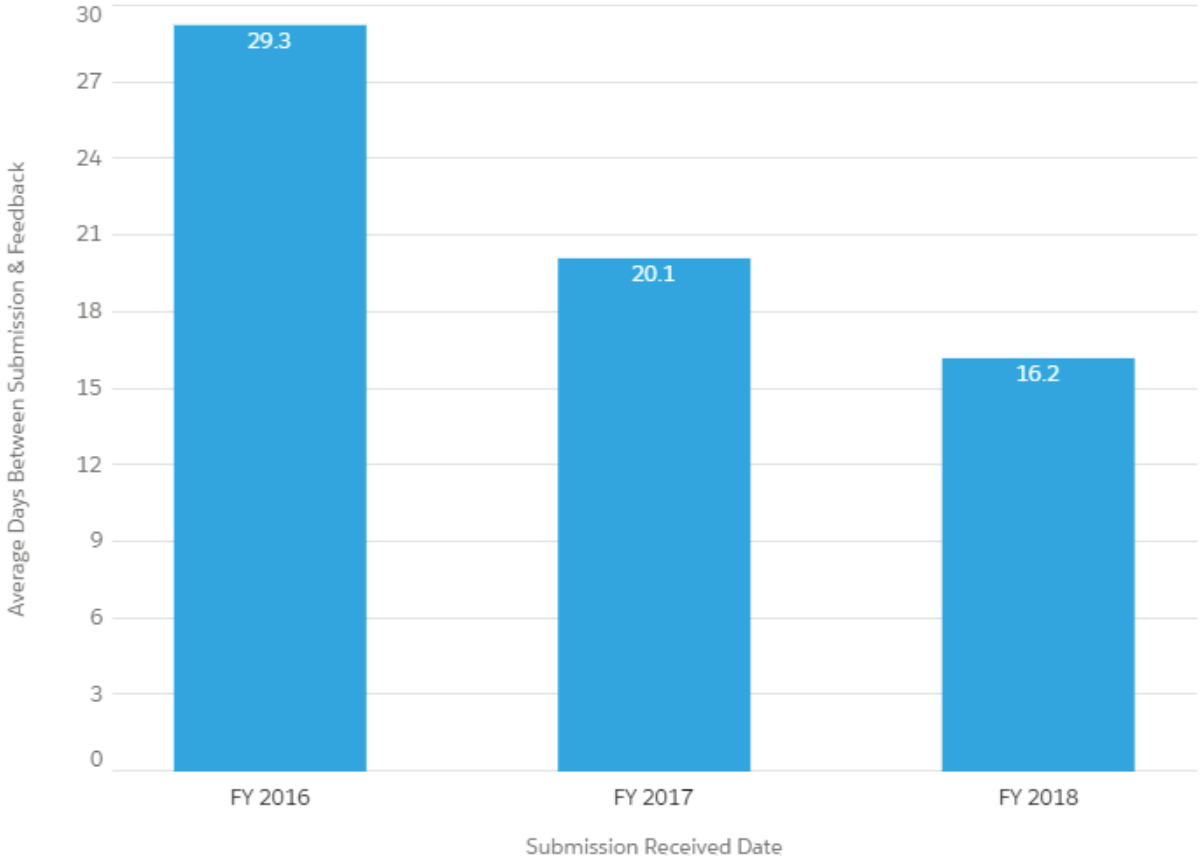


3.3. ISAC update

Over the course of the 2018/19 reporting year, further work has been undertaken to streamline and refine parts of the ISAC review process, which has had a positive impact on the time taken to review protocols.

ISAC aims to make a decision on submitted applications within 28 working days. This target is defined as the time between an application being successfully submitted to ISAC and the decision on that protocol being communicated to the applicant. Figure 9 shows that the average time taken to communicate a decision on submitted applications in 2018/19 was just over 16 working days. This figure is 19% lower than the average time for the 2017/18 reporting period, and almost half the average time taken in 2016/17.

Fig. 9 – Average working days between protocol submission and feedback sent date between financial years 2016/17 and 2018/19



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 decreased by just under 10%. This is despite a 57% increase in the number of amendments submitted to ISAC in 2018/19 compared to the previous financial year. The 16% reduction in resubmissions indicates that more protocols are being approved first-time. In fact, the proportion of protocols rated as 'Approved' or 'Approved with Comments' at first review was 38% in 2018/19, up from about 15% in the previous reporting year.

Of the 336 protocols approved in the reporting period, over 50% were led by UK academic institutions, with disease epidemiology research remaining the most prevalent research type.

Data linkage remains an important CPRD service, with 263 of the 336 protocols approved in the reporting period requesting linkage to one or more other data sources.[7]

[7] Figure correct at time of writing

Annex 1 – Membership over 2018/19 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 (Reappointed as Deputy Chair in April 2018)
Associate Professor, Medical Statistics Group, Nuffield Dept of Primary Care Health Sciences, University of Oxford

Dr Angelyn Bethel MD (Reappointed 1 January 2018)
Deputy Director, University of Oxford Diabetes Trials Unit

Professor Sinead Brophy BSc PhD (Reappointed 1 January 2018)
Professor of CIPHER, College of Medicines, Swansea University

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 Duncan Edwards BSc, MB BS, MRCGP (Reappointed 1 March 2018)
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 fPROMS1 January 2018)
Senior Lecturer in Social Epidemiology, University of Liverpool

Dr Wendy Knibb MSc (Econ.) PhD (Health Econ.) (Reappointed 30 September 2017)
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 (Reappointed 5 November 2018)

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 (Reappointed 30 September 2017)

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)

NIHR Clinical Lecturer, Centre for Primary Care and Public Health, Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London

Dr Jennifer Quint PhD (Reappointed 1 January 2018)

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 (Reappointed 1 March 2018)

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 (Reappointed 1 January 2018)

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 (Reappointed 1 January 2018)

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 has worked 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.

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.

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 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.

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.

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 (2018/19)

	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	UCB	Grant funding	
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
Prof Peter Helms	None	N/A	None	N/A	
Dr Caroline Jackson	None	N/A	None	N/A	

	Personal Interests		Non-Personal Interests		Current Interest
Member	**Name of Company**	**Nature of Interest**	**Name of Company**	**Nature of Interest**	
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 Williams (joint supervisor with GSK)	Yes

	Personal Interests		Non-Personal Interests		Current Interest
Member	**Name of Company**	**Nature of Interest**	**Name of Company**	**Nature of Interest**	
				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

Annex 4 – ISAC Audit Project

ISAC "audit" project

Presented, on behalf of ISAC, by

Richard Stevens
Director, M.Sc. in EBHC Medical Statistics
University of Oxford

Research question and aims

- Motivated by a proposal from a CPRD researcher,
- ISAC compared papers published in 2013 to their protocols.

Primary research question

As of 2013, how closely do CPRD users follow ISAC protocols?

Motivation

1. Understand current practice.
2. Establish a baseline against which future practice can be measured e.g. following any changes to procedures or training.

Methods

- All CPRD papers published in 2013 were identified, and their corresponding protocols.
- An ISAC member compared each paper to the protocol.
- Non-trivial changes -> discussion by ISAC and with authors.
- Note: no established definition of "major change" existed until 2012.

Methods: definition of major change (2014)

- A difference between an approved protocol and the resulting publication will be considered a major deviation if it clear that such a difference would have required the submission of an amendment, no such amendment having been submitted. Submission of an amendment is required if the alteration(s) made substantially change the study design or analysis plan of the proposed research.
- Examples:
  - A change to the primary hypothesis being tested in the research
  - A change to the design of the study
  - Additional outcomes or exposures unrelated to the main focus of the approved study
  - Non-trivial changes to the analysis strategy
  - Change of principal investigator
  - Use of additional linkages to other databases
  - Any new proposal involving contact with health professionals or patients or change in regard to such matters

- 133 protocol/papers included.
- 22 potential major deviations identified by first reviewer.[8]
- 4 of these not confirmed.
- 18 (13.5%) papers were sufficiently different from the protocol that *under current guidance* a major amendment to the protocol would be required.

	Final classification
No deviation	40
Minor deviations	75
Major deviations	18
TOTAL	133

Discussion

- Prior to 2013, a small number of projects deviated from protocol to an extent that we would not now consider minor.
- Limitations:
  - No explicit definition of major amendments existed at the time these protocols were written;
  - Older protocols varied greatly in content and level of detail – harder to assess.
- This project has helped ISAC and CPRD make changes:
  - to ISAC guidance,
  - to ISAC protocol headings,
  - to ISAC application form,
  - and to website,
- all designed to promote adherence to a better-defined standard of agreement.

Major Recommendations

1. ISAC guidance on major and minor amendments.
   - First published 2012
   - Current version published 2014
2. From 1st April 2014 CPRD manuscripts are required to state
   - the ISAC protocol number, and
   - that the protocol has been made available to reviewers at the journal.

[8] This footnote has been added for the annual report. The slides presented at the CPRD User Group meeting reported that these 22 were identified “by first reviewer”. This should read, “identified by ISAC”