Medicines & Healthcare products Regulatory Agency

CPRD

Independent Scientific Advisory Committee (ISAC)

Annual Report

1 April 2019 to 31 March 2020

NIHR | National Institute for Health Research

Contents

Glossary

CAG	Confidentiality Advisory Group
CPRD	Clinical Practice Research Datalink
CPRD Aurum	CPRD primary care database sourced from EMIS® practices
CPRD GOLD	GP On-Line Database (CPRD primary care database sourced from Vision® practices)
EHR	Electronic Healthcare 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 Chair of ISAC

I welcome the publication of the ISAC Annual Report for the 2019-2020 reporting period, the fifth Report in my role as Chair of ISAC. The report reflects another busy year for the Committee, and I am grateful for the tireless work of members during this time. I am also thankful to all the applicants who continue to stimulate us by the depth and breadth of their proposals, which highlight the versatility of public health applications of CPRD data.

The twelve months covered by this Report have seen a slight reduction in the number of new research protocols received, down 12% compared to the previous reporting period. There have been no protocol rejections within the reporting period, and the number of resubmissions has decreased by 32% from 2018-2019. We continue to see an increase in the number of amendment applications received for approved protocols, up by 15% compared to last year, which reflects the number of ongoing studies utilising CPRD data. We are also seeing uptake of data from the new CPRD Aurum database, with around 40% of all applications submitted during the reporting period requesting access to CPRD Aurum.

Average time for feedback on applications continues to decrease, down 20% from the previous reporting period and meaning that, on average, feedback is provided in just over 13 days from submission. This is less than half the time taken in the 2016-2017 reporting year and is a testament to the efficiency of the Committee and supporting CPRD team.

The success of the ISAC is dependent on the voluntary commitment of Committee members. I would like to thank them for their continuing contributions during this reporting period. I would also like to share my particular thanks to Dr Duncan Edwards, who completed his term of office during the reporting period, and to Sally Malin and Marcia Saunders for their contributions to the May 2019 meeting.

I would like to thank Dr Ian Hudson, Dr June Raine and Sir Michael Rawlins for their commitment to the work of ISAC. I remain grateful for the tremendous support we receive from CPRD, its team of researchers 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 Sam Speer, and Ms Claudia Hafford-Tear, who provide the primary secretariat function for the Committee and facilitate the management and review of research applications. I look forward to working closely with the ISAC membership and CPRD team in coming year.

Professor Deborah Saltman AM
Independent Scientific Advisory Committee (ISAC)

1. Introduction and background

1.1. Introduction to the report

The Medicines and Healthcare products Regulatory Agency (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 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 research proposals seeking to use CPRD data, including primary care data linked to other health-related data sets.

This Annual Report presents an overview of the CPRD database, research data governance, ISAC outputs and membership of the Committee, for the period 1 April 2019 to 31 March 2020.

1.2. Clinical Practice Research Datalink

1.2.1. The CPRD database

The CPRD database offers a quality-assured source of longitudinal, near real-time health data that is representative of the UK population. CPRD primary care data are sourced from a UK-wide network of 1,550 GP practices across the UK. The CPRD database contains anonymised primary care electronic health records (EHR) on more than 50 million patients, of which 14 million are currently registered at contributing GP practices. Patient records 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

CPRD data are used worldwide by regulators, academic researchers and the life science industry for observational and interventional public health and clinical studies. Over 2,400 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.

1.2.2. Permissions and approvals to safeguard patient data

CPRD has NHS HRA REC approval to allow the collection and release of anonymised primary care data for observational research. [NHS HRA REC reference number: 05/MRE04/87]

Each year CPRD obtains Section 251 regulatory support through the Confidentiality Advisory Group (CAG), to enable patient identifiers, without accompanying clinical data, to flow from contributing GP practices to NHS Digital, for the purposes of data linkage. [CAG reference number: ECC5-05(a)/2012]. Linkage of secondary health related datasets to primary care data greatly enhances the capacity for public health research. The use of NHS Digital, the statutory body in England permitted to receive identifiable patient data, for data linkage ensures that CPRD itself never receives identifiable patient data.

As an organisation that has access to anonymised patient data, CPRD also completes an annual Data Security and Protection Toolkit to confirm that CPRD's data security standards align with 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 that their data is being collected by CPRD to support public health research and that they can opt-out of their data being shared with CPRD. CPRD does not collect data from 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 that have been anonymised in accordance with the Information Commissioner's Office Anonymisation Code of Practice. 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

The ISAC is comprised of scientific experts, who provide advice on the medical, statistical/epidemiological, and methodological aspects of protocols submitted to the Committee for review.

2.2.1. Membership over the reporting period

At the end of the reporting period, ISAC membership consisted of 18 members, including the Chair. A total of 19 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 2019 and 31 March 2020 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: 02 May 2019, and 28 October 2019. ISAC meetings were held at the MHRA offices located at 10 South Colonnade, Canary Wharf, London E14 4PU.

2.3.2. Member meeting expenses

During 2019/20 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 CPRD researchers, who perform an initial assessment of the application's feasibility and a screening for risks relating to the proposed research. The application and CPRD researcher assessment are then passed to the Committee Chair for review. CPRD researchers will carry out a scientific review of protocols deemed to be routine research and the Committee carry out a scientific review of protocols which are considered non-routine. Non-routine research applications propose research of major public health importance/implications, high public health or reputational risks or use of novel methodology to address important health questions.

When reviewing CPRD protocols, the Committee and CPRD researchers considers whether:

- the CPRD database is a suitable data source for the proposed 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 practice and patient confidentiality is protected.

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 reviewer feedback in their re-submitted application. All resubmissions are reassessed by the ISAC Chair and the final decision is 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 the CPRD website once the Committee has agreed the full minutes. The summary ISAC minutes are available at https://cprd.com/ISAC-minutes-annual-reports. The annual reports of ISAC are made available on the CPRD website, at https://cprd.com/ISAC-minutes-annual-reports.

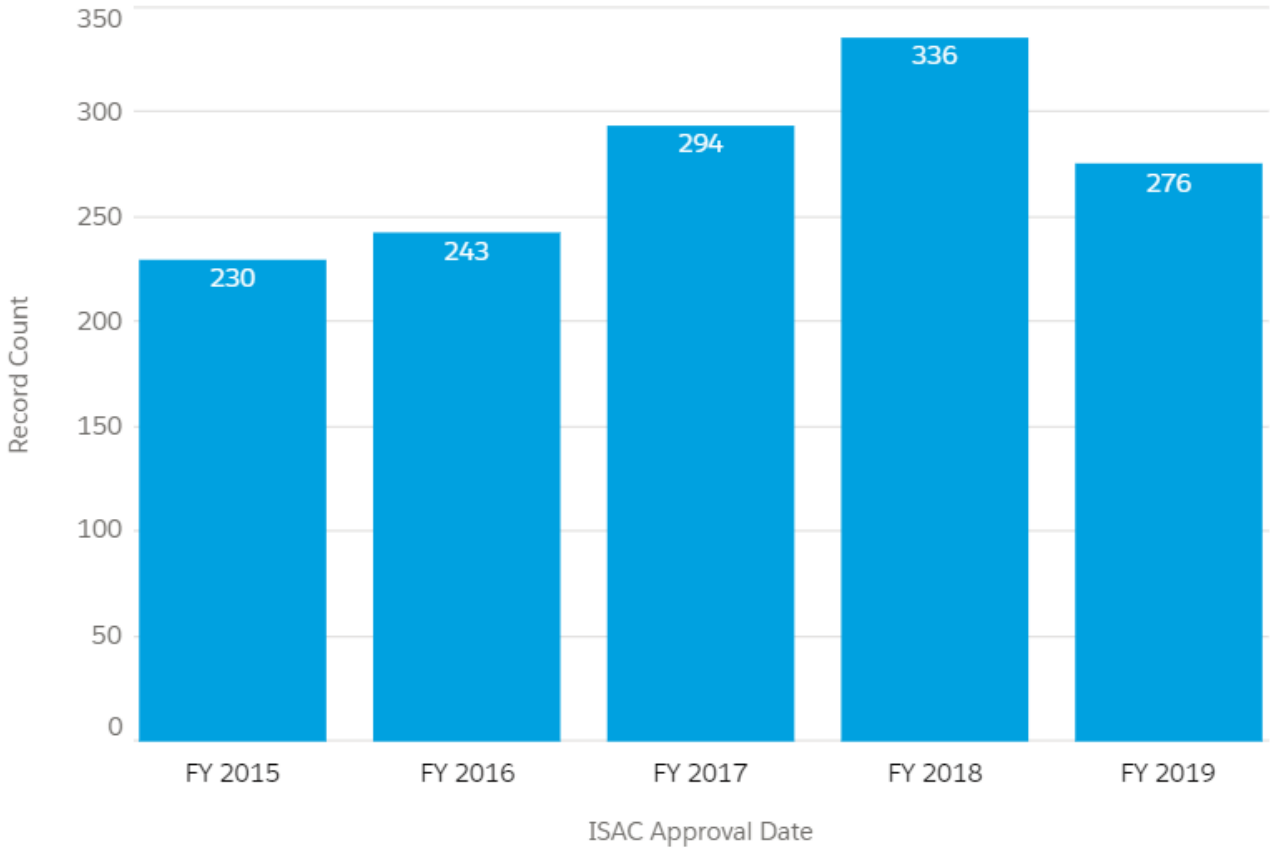
3. Activities and Outputs

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

ISAC approved 276 applications in the reporting period[1] (Fig. 1), a decrease of around 18% on the previous 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.

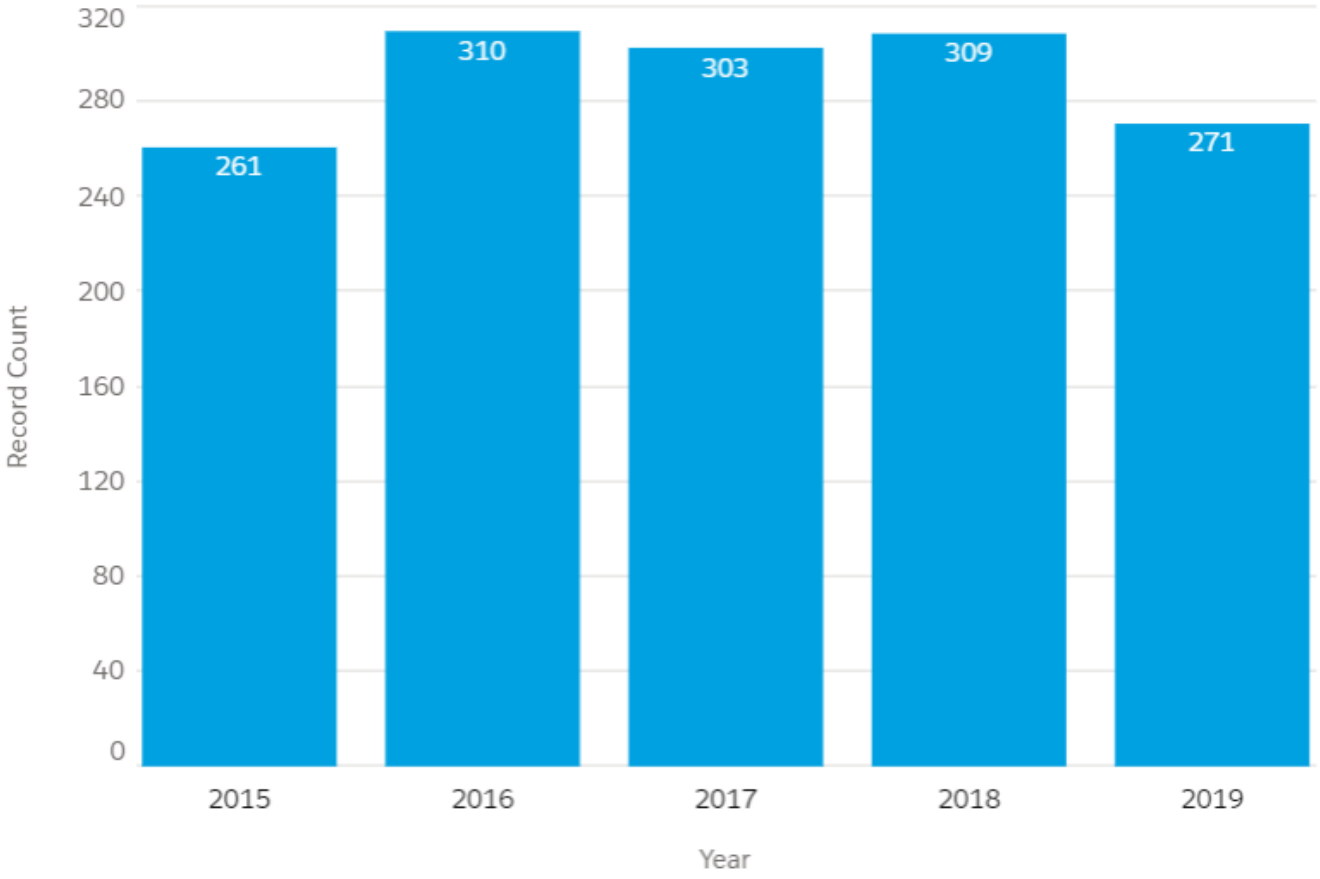
Fig. 1 – Research applications approved between financial years 2015/16 and 2019/20



[1] 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.

A total of 271 new research protocols requesting access to CPRD data were received in 2019/20, a 12% decrease on the previous financial year from 309 (Fig. 2)[2]. The figure is obtained by counting protocols that have a 'submission received' date within the given financial year.

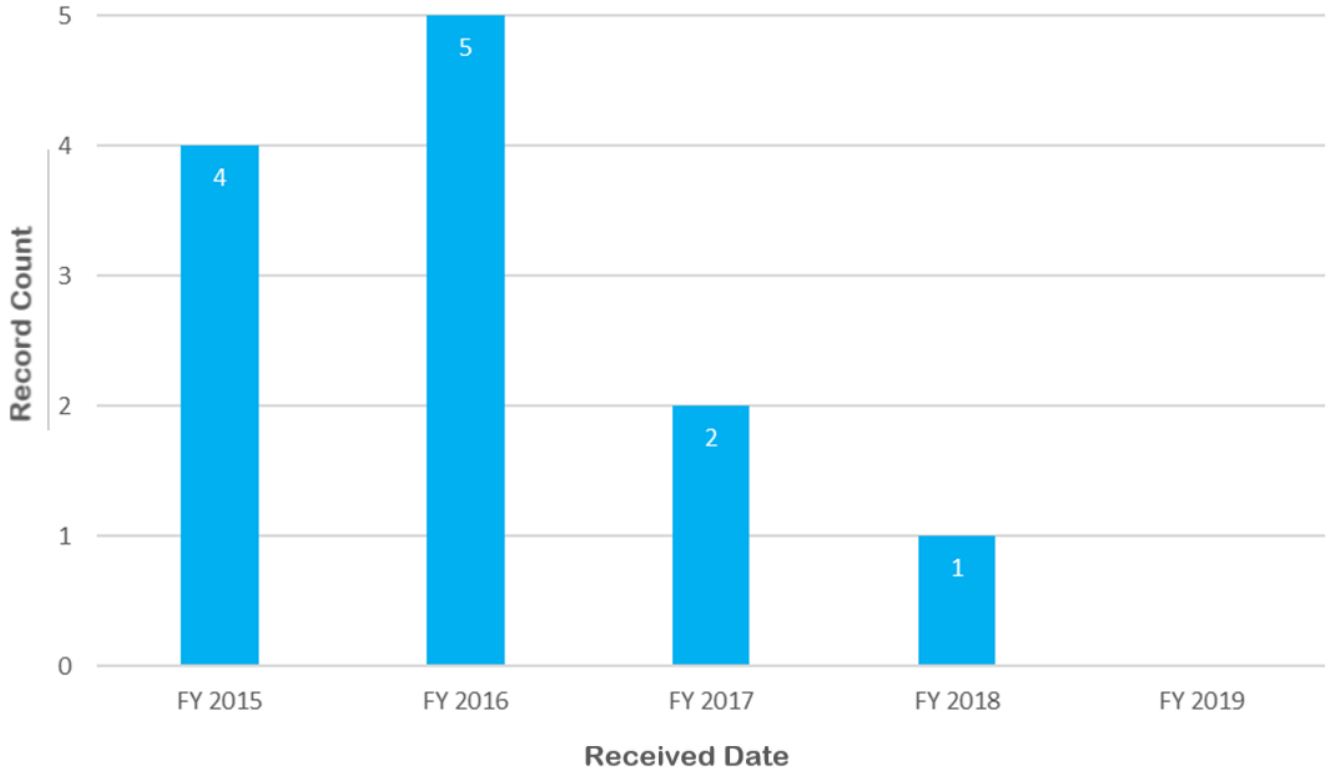
Fig. 2 – New research applications received between financial years 2015/16 and 2019/20



[2] 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.

ISAC did not reject any applications within the reporting period (Fig. 3).

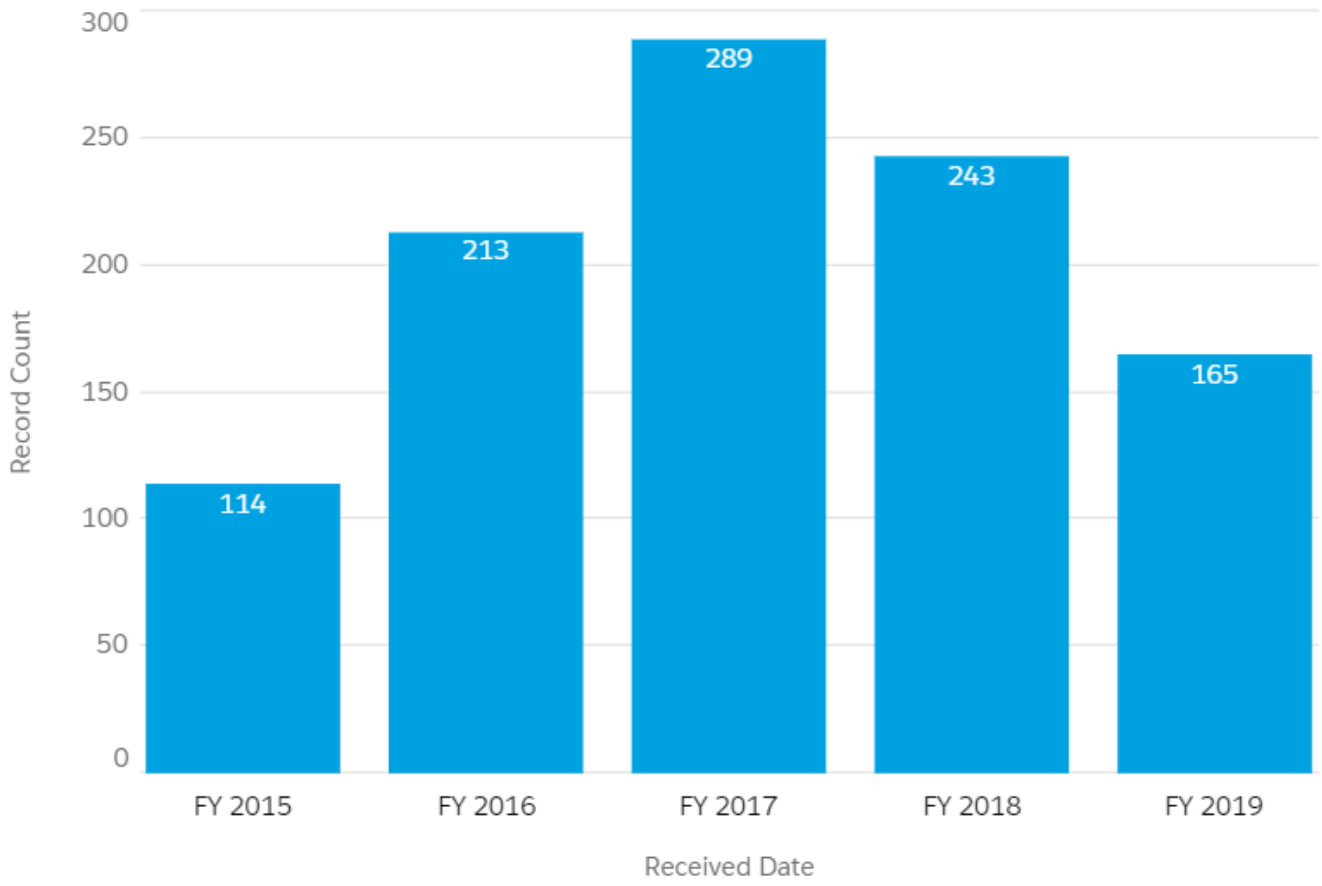
Fig. 3 – Research applications rejected between financial years 2015/16 and 2019/20



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.

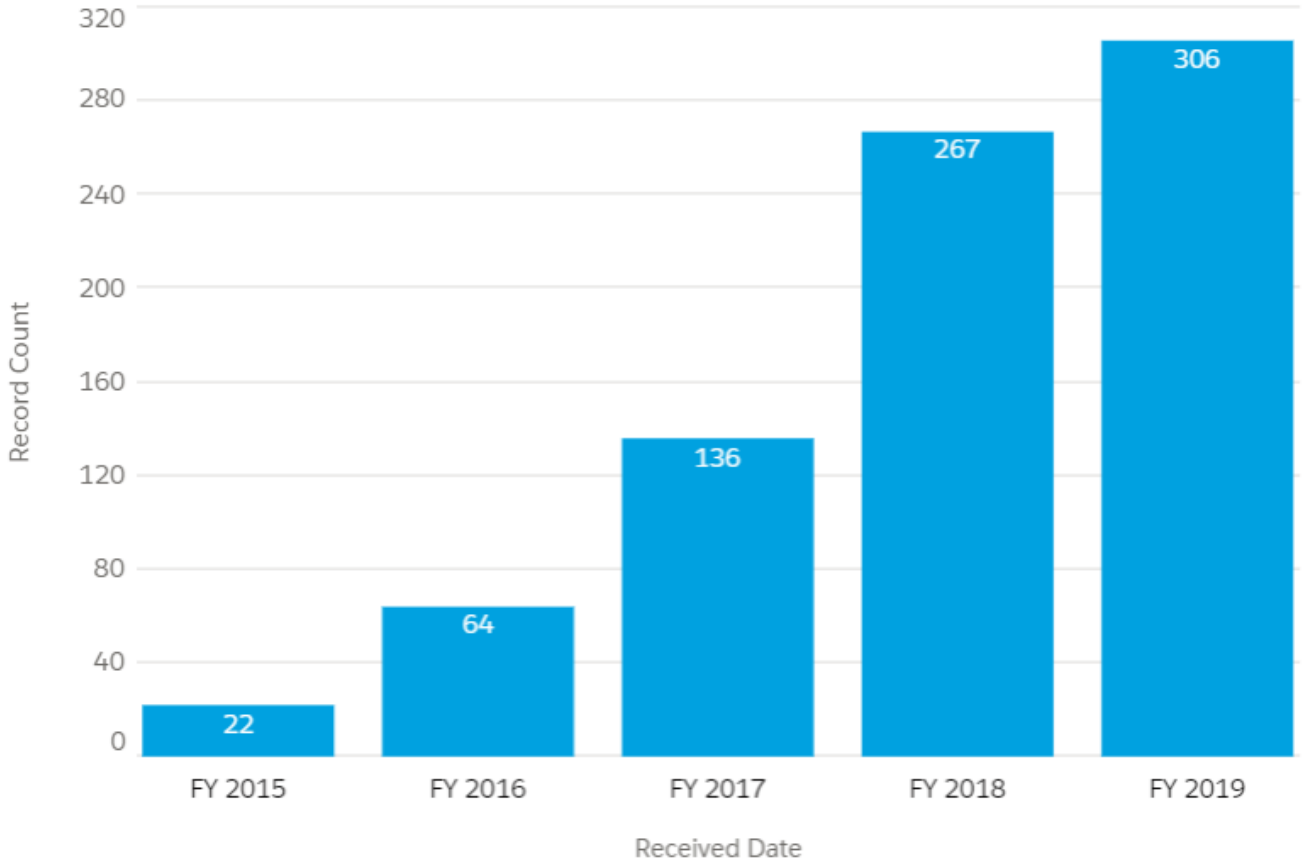
CPRD received 165 resubmissions in the reporting period (Fig 4), a 32% decrease compared to the previous year. The decrease may partly be due to the drop in new submissions during the reporting period, but there has also been a decrease in the number of protocols requiring resubmission. In the 2018/19 reporting period, over 60% of newly submitted protocols were rated as ‘resubmission required’ after first review, dropping to 52% in the current reporting period. Furthermore, there were fewer second and third resubmissions than in previous years.

Fig. 4 – Resubmissions received between financial years 2015/16 and 2019/20



306 amendments to previously approved protocols were received in the reporting period, a 15% 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 2019/20



In total, ISAC made 640 decisions during the reporting period, down 7% on the previous year; 259 of these were decisions relating to protocols, and 381 were decisions relating to resubmissions and amendments.[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 276 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, 2019/20[4]

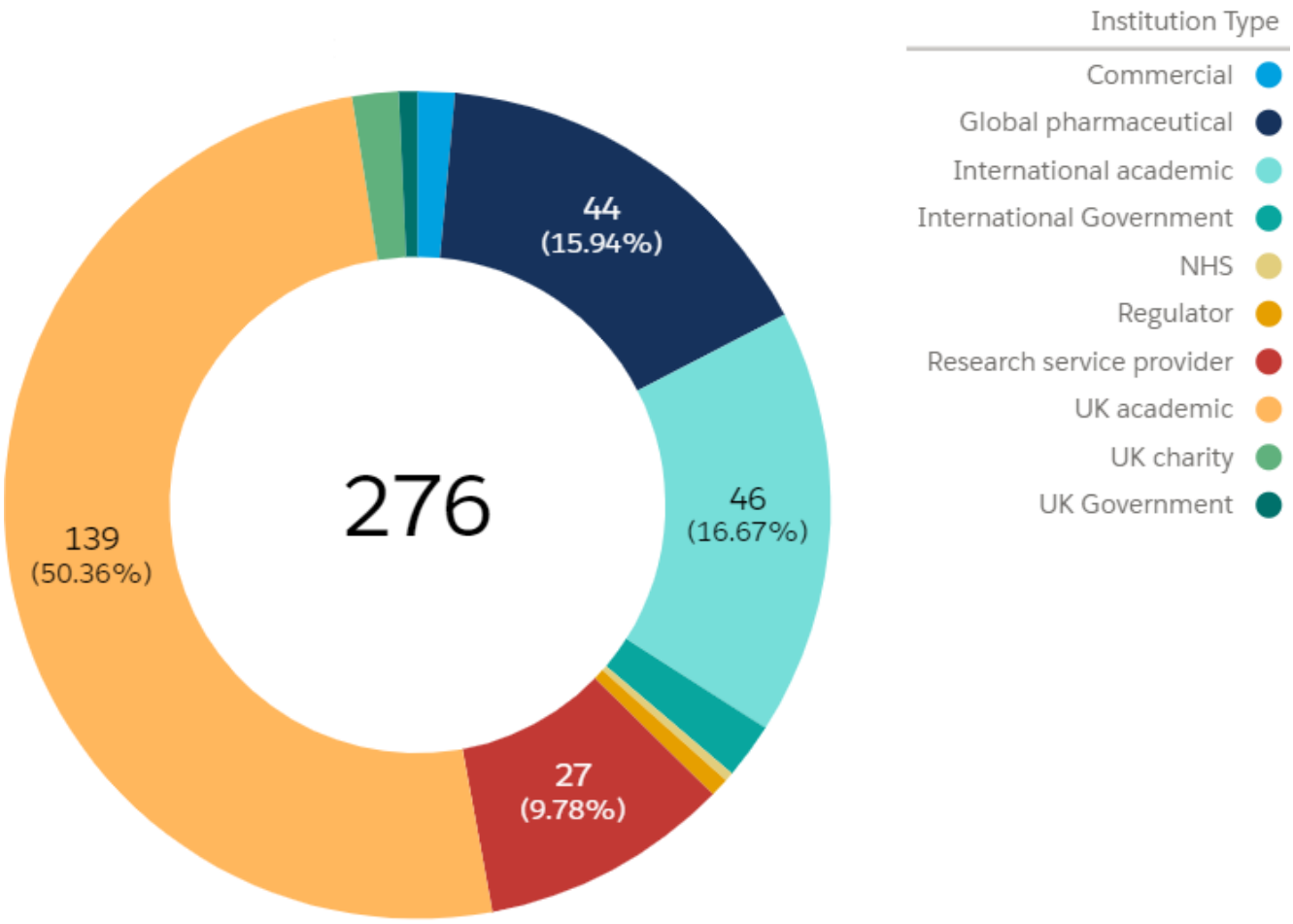
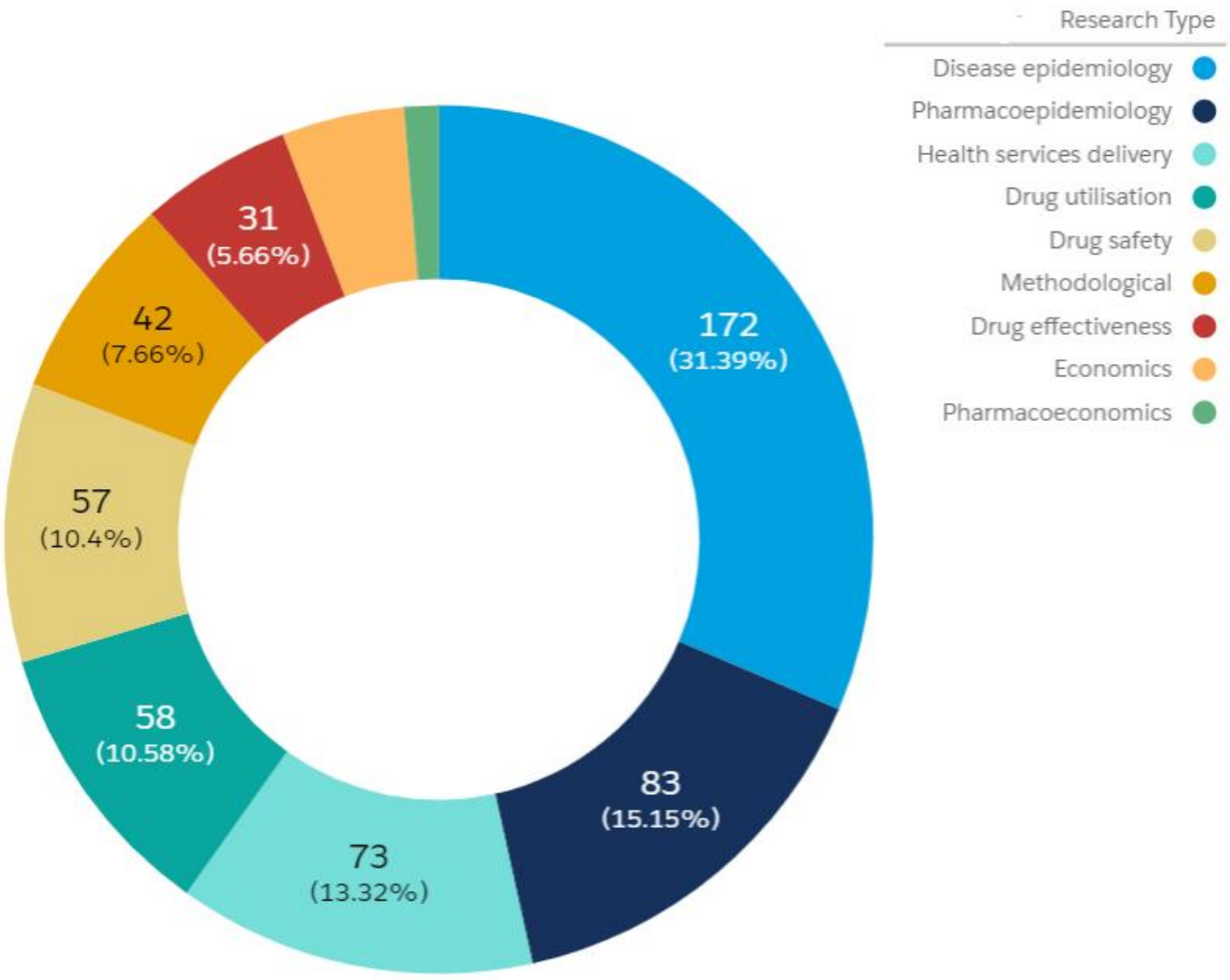


Figure 7 provides an overview of the 276 approved protocols, categorised by research type. A protocol may be assigned to more than one study type by the applicant. The Figure shows that most applicants describe their research as disease epidemiology.

[4] Figures not shown: Commercial, 4 (1.45%); UK Charity, 5 (1.81%); Industry SME, 1 (0.36%); NHS, 1 (0.36%); Regulator, 2 (0.72%); International Government, 6 (2.17%); UK Government, 2 (0.72%).

Fig. 7 – Approved protocols by research type 2019/20[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.

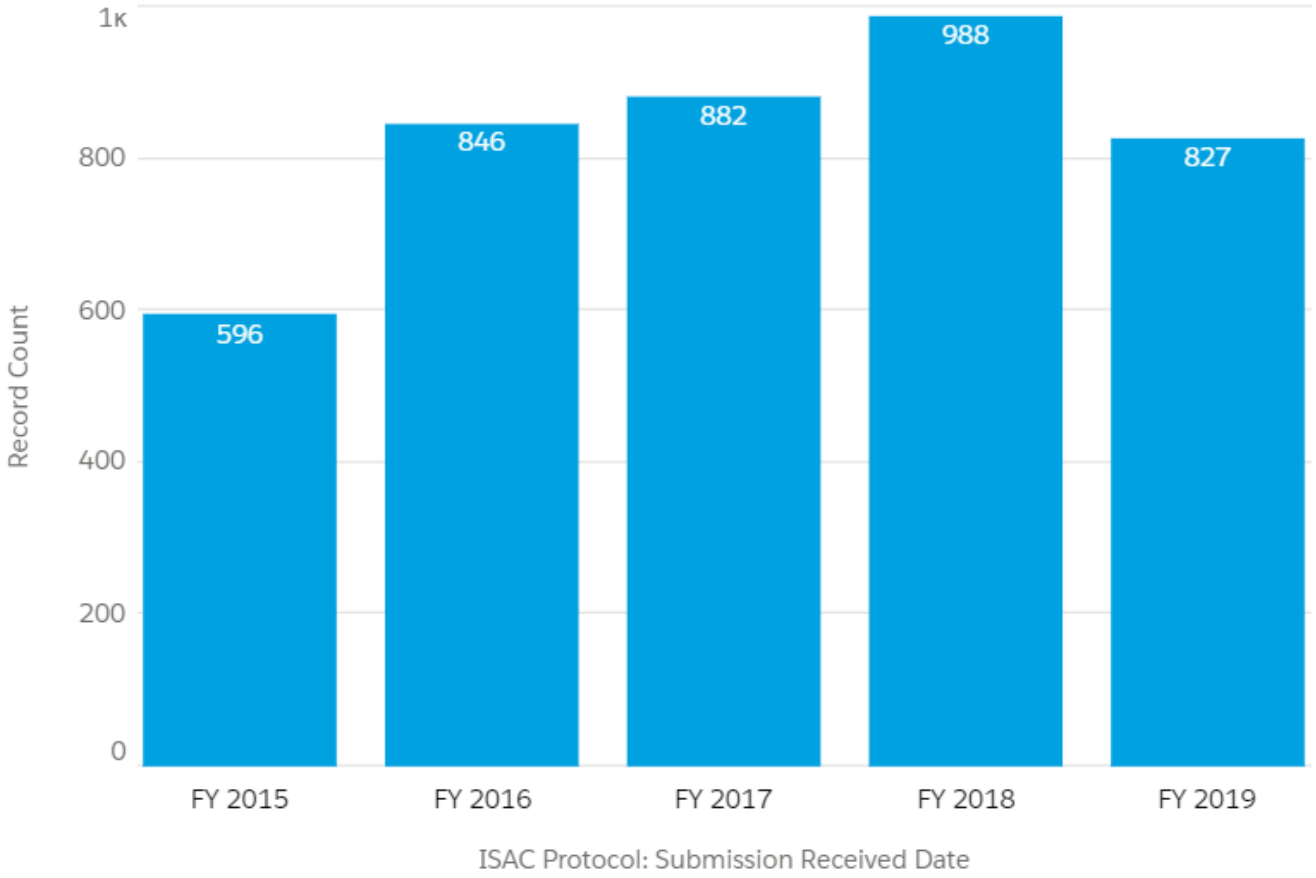
A significant proportion of protocols submitted to ISAC request linkage to other datasets. Figure 8 shows that the 271 new applications submitted to ISAC in the 2019/20 reporting period represented 827 linked datasets being requested[6]. The data show that, on average, around three linkages are

[5] Figures not shown: Drug Effectiveness, 31 (5.66%); Economics, 25 (4.56%); Pharmacoeconomics, 7 (1.28%). 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.

requested for each protocol submitted, and continues to highlight the importance of CPRD's data linkage service. While this number is smaller than in recent years, part of this can be explained by receiving fewer new applications during the reporting period. The figure is likely to increase over the coming years as linkages are added to ongoing studies via amendments.

Fig. 8 – Linkages requested in ISAC applications submitted between financial years 2015/16 and 2019/20

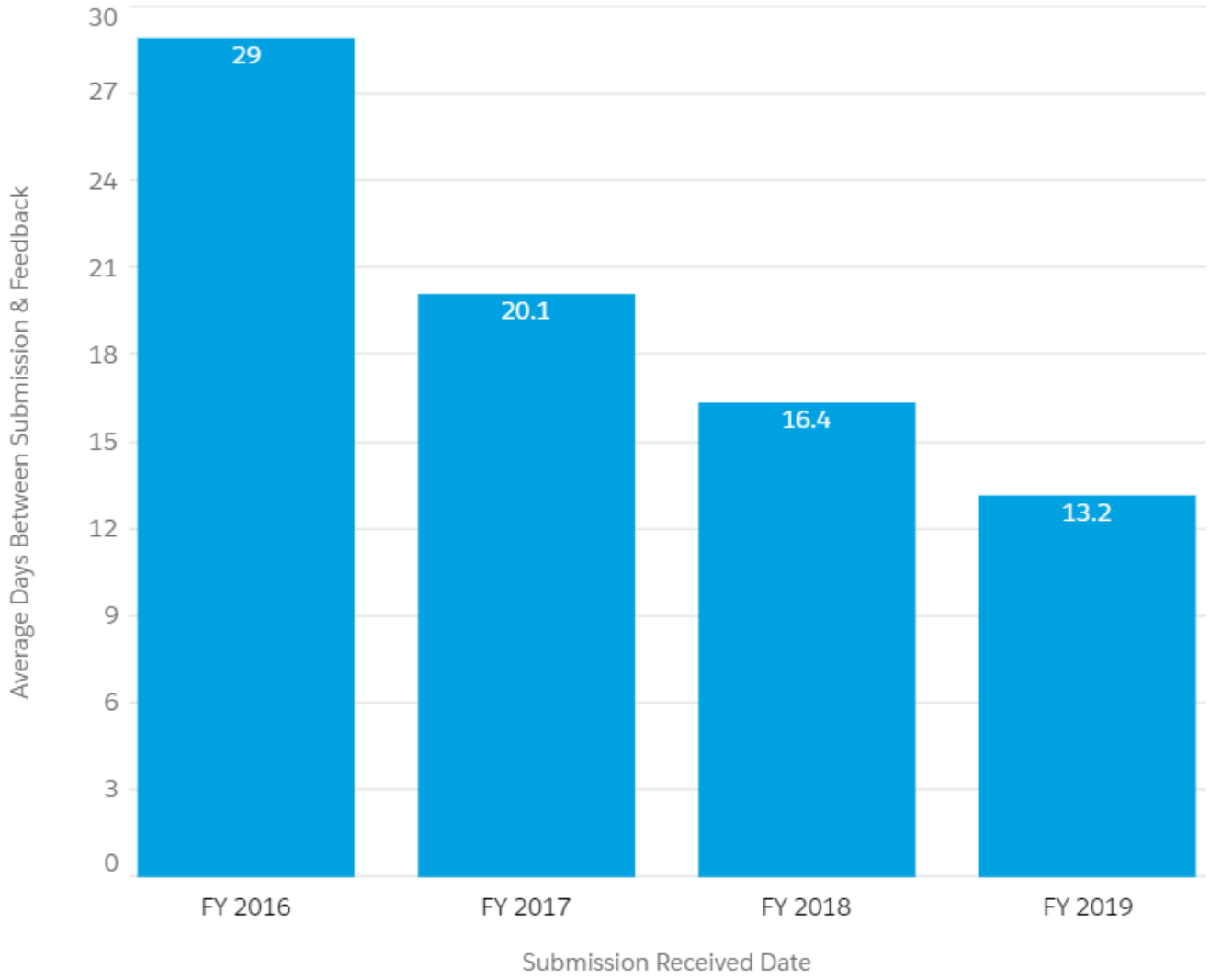


3.3. ISAC update

Over the course of the 2019/20 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 2019/20 was just over 13 working days. This figure is 20% lower than the average time for the 2018/19 reporting period, and less than 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 2019/20



3.4. Summary

In summary, the number of new ISAC applications decreased slightly from the previous reporting year. Accordingly, the workload for ISAC decreased by just under 7%. The decrease may be explained by the increasing number of applications for programmes of work. This would also account for the further increase in amendments, as changes are made to ongoing studies. During the reporting period there have also been changes to the application form and guidance to improve clarity, and as a result there has been a 30% decrease in the number of protocols requiring resubmission. In fact, the proportion of protocols rated as ‘Approved’ or ‘Approved with Comments’ at first review was 47% in 2019/20, up from about 38% in the previous reporting year.

Of the 276 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 214 of the 276 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 2019/20 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

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

Dr Rosie Cornish (Appointed 17 January 2017)
Senior Research Associate, Population Health Sciences, Bristol Medical School, 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 Evangelos Kontopantelis PhD (Appointed 1 January 2017)
Professor and Data Sciences Health Services Researcher, Division of Informatics, Imaging and Data Sciences, University of Manchester

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)
Professor of Statistical Genetics. Division of Musculoskeletal & Dermatological Sciences, University of Manchester.

Professor Keith Neal (Reappointed 30 September 2017)
Emeritus Professor in the Epidemiology of Infectious Diseases, University of Nottingham and Consultant in Health Protection, for the Programmed Delivery Unit, 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

Professor Jennifer Quint PhD (Reappointed 1 January 2018)
Professor of Respiratory Epidemiology, National Heart and Lung Institute, Imperial College London

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, NHS National Services Scotland

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.

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 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. She works on both applied and methodological projects, with a particular focus on analyses in the presence of missing data and the use of administrative and routine health data in research.

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 Evangelos Kontopantelis is a Professor and Data Sciences 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.

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 a Professor of Statistical Genetics in the Centre for Genetics and Genomics Versus Arthritis at the University of Manchester, and has visiting appointments at the Estonian Genome Centre, University of Oxford, University of Liverpool, and Helmholtz Centre Munich. 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 (renewed in 2012). 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 and glycaemic traits, kidney function, and blood pressure.

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.

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

Professor 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 National Services 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 (2019/20)

	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 Krishnan Bhaskaran	None	N/A	None	N/A	
Prof Sinead Brophy	None	N/A	UCB	Grant funding	
Dr Iain Carey	None	N/A	None	N/A	
Mrs Rosie Cornish	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 Evangelos Kontopantelis	None	N/A	None	N/A	
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	None	N/A	None	N/A	
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

	Personal Interests		Non-Personal Interests		Current Interest
Member	**Name of Company**	**Nature of Interest**	**Name of Company**	**Nature of Interest**	
			IQVIA	Consultancy	Yes
Prof Martin Tobin	None	N/A	GSK	BBSRC CASE studentship to Alex Williams (joint supervisor with GSK) Respiratory Genomic Collaboration with University of Leicester (co-investigator)	Yes
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

	Personal Interests		Non-Personal Interests		Current Interest
Member	**Name of Company**	**Nature of Interest**	**Name of Company**	**Nature of Interest**	
	Jacobson Pharmaceutical (Hong Kong)	Consultancy			Yes