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The General Practice Research Database

Role in Pharmacovigilance

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Abstract

The General Practice Research Database (GPRD) is the world's largest computerised database of anonymised longitudinal clinical records from primary care. The database already has an international reputation in the field of drug safety signal evaluation where the results of GPRD-based pharmacoepidemiological studies have been used to inform regulatory pharmacovigilance decision making. The characteristics and richness of the data are such that the GPRD is likely to prove a key data resource for the proactive pharmacovigilance anticipated in risk management and pharmacovigilance plans.

An update of recent developments to the database and new data available from it – including spontaneously recorded suspected adverse drug reactions – is presented in the article, with a description of how the data can be used to support a variety of pharmacovigilance applications. The possibility of using the GPRD in signal detection and assessment of the impact of pharmacovigilance activities in the future is also discussed.

Pharmacovigilance encompasses the processes by which medicines are monitored long-term to identify and evaluate possible safety hazards ('signals') and subsequent action taken to optimise the benefit-risk balance of drugs by preventing or minimising risks to patients and ensuring safe and effective use. It is a rapidly evolving discipline, which is acquiring an increasingly high profile within medicines regulatory and wider public health circles, as well as in the media. Sub-specialities such as risk communication are being developed and broader stakeholder involvement encouraged. New methodologies, e.g. statistical approaches to signal detection based on spontaneous reporting, have been implemented. Regulators and the pharmaceutical industry have been collaborating under the auspices of the Council for International Organizations of Medical Sciences (CIOMS) and the International Conference on Harmonisation (ICH) to enhance and standardise exchange of pharmacovigilance data. A wholistic scientific model for pharmacovigilance,[1] characterised by best evidence-based decision making and multi-disciplinary working, has been embraced widely.

Emerging international consensus that public health would be better protected by early planning for proactive pharmacovigilance activities for the postmarketing phase and more formalised agreement of risk management strategies[2-4] is likely to have a major impact on pharmacovigilance. Epidemiology will play an ever greater role in pharmacovigilance as prospective postmarketing observational studies become the norm.

The GPRD has a proven track record as a key resource for pharmacoepidemiological studies and has been used internationally to inform regulatory pharmacovigilance decision making.

The epidemiological data available from the GPRD and their use to support pharmacovigilance applications are presented in this article, which also includes an update on recent developments to the database. The possibility of using the GPRD for signal detection and assessing the impact of regulatory action is discussed.

1. Overview of the General Practice Research Database (GPRD)

Formerly known as the Value Added Medical Products (VAMP) Research Databank, the GPRD was created in 1987 and donated to the UK Department of Health in 1994. The history of the development of the database has been described elsewhere.[5,6] Since April 1999 it has been managed by the Medicines Control Agency (MCA), which became in April 2003 the Medicines and Healthcare products Regulatory Agency (MHRA), and is operated on a not-for-profit basis by the GPRD Division, a dedicated Division of the Agency, which delivers GPRD-related services to researchers inside the Agency and external users.

The GPRD is the world's largest computerised database of anonymised longitudinal clinical records from general practice, comprising over 35 million patient-years worth of data collected from approximately 8.9 million patients.

Table I shows the large number of events captured in the database. Although the GPRD is most widely known internationally as a resource for pharmacoepidemiology,[7] it has been used for a wide variety of public health applications and these are expanding. These include incidence and prevalence of disease (e.g. ischaemic heart disease,[8] COPD[9] and bone fractures[10]), drug utilisation (e.g. treatment patterns in newly diagnosed heart failure,[11] switching between metered dose inhalers and drug powder inhalers[12]), pharmacoeconomics (e.g. cost of acute exacerbations of chronic bronchitis[13] and migraine therapy[14]), use of health service resources (e.g. association of air pollution with consultations for asthma,[15] hospitalisations due to hypoglycaemia[16]). Research based on GPRD data has generated over 350 papers in peer reviewed journals (see bibliography at: http://www.gprd.com/html/bibliography.htm).

Table I. Events captured in the Full Feature General Practice Research Database (GPRD)

Event type	Number of events (million)
Clinical	251
Consultation	301
Immunisation	28
Referral	20
Tests	76
Prescriptions	305
repeats	38

1.1 Data Collection

In the UK, general practitioners (GPs) act as the gatekeepers to healthcare delivery via the National Health Service (NHS), which provides cover for the whole population from "cradle to grave". Fortuitously, this has enabled the development of several important databases and research methodologies including the GPRD, the Medicines Monitoring Unit (MEMO) database,[17] the IMS Health database MediPlus[18] and the prescription event monitoring (PEM) methodology of the Drug Safety Research Unit[19] and established the UK as an important focus for longitudinal primary healthcare data and for multidisciplinary public health research.

Anonymised patient clinical records for the GPRD are collected from a voluntary group of GPs throughout the UK who use a clinical system software supplied by In Practice Systems Ltd in their practices. Individual patients are identified to researchers by encrypted and unique numerical codes, which are only decodeable by the practice. Individual practices are distinguished in the dataset by encrypted unique identifiers; practice identities are not revealed to researchers using the database. Contributors are required to provide data of a high degree of completeness and receive a small fee for their services in providing data. Currently, data are being collected incrementally from roughly 3 million patients in 380 practices on approximately an

Table II. Data collected for the General Practice Research Database (GPRD)

Data category	Elements
Patient demographics and registration details	Birth year, month of birth for patient <15 years, gender. Accurate patient registration history at practice including registration status (e.g. permanent, transferred out) transferred out reason (e.g. death) and dates. Health authorities now maintain a central register of registrations which ensures that practice details are accurate
Therapy (medicines, vaccines, devices)	Prescriptions issued by the practice coded by drug substance or product using Multilex®.[a] Dose, route of administration, daily quantity, number of packs, pack size, prescription duration, repeats. (Indication for therapy is available by cross-referencing against the medical entry during the same consultation)
Practice details	Start date of electronic data recording, all GPRD data collection dates, NHS region
Patient – lifestyle factors	Smoking status, smoking details (number of cigarettes, cigars, units of tobacco per day) – recorded in 37.2% of 18–90 year olds in the GPRD population
	Alcohol consumption (units per day/week), recorded in 51% of patients
	Weight, height, body mass index, exercise pattern and diet
Medical diagnoses, including comments[b]	Coded using Read Terms,[c] which are mandated for use by GPs in the UK. Event date
Referrals to hospitals or specialists	Date, reason (Read coded), referral department, NHS speciality, referral urgency (routine etc.), referral type (outpatient etc.), role of staff member making referral (GP, nurse, etc.)
Treatment outcomes	Hospital discharge summary cases where patient was referred to hospital for treatment. (Anonymised post-mortem details, death certificates, hospital discharge letters available on project basis, disease-specific questions)
Laboratory tests, pathology, etc.	Date. Qualitative description. Results (value and units). Normal range in the laboratory
Consultations	Unique consultation identifier and duration of consultation

a Prescriptions for controlled drugs and those issued on home calls are hand written. (A recent study [not based on GPRD practices] indicates that about 80% of this information is entered into the patient's electronic record.[20])

b The free text comments provide additional information and in some cases can be used to confirm or refute a recorded diagnosis. It is not possible for the GPRD Division to include this field in the database as there is a possibility that it may contain confidential information, if the GP has not used the software available in the Vision clinical system software to prevent such text collection. However, the GPRD Division offers a service in which the comments related to specific medical or therapy records can be searched for key words or extracted and anonymised manually.

c Use of Read Clinical Terms is currently mandated in UK GP computer systems. Historically GPs using VAMP software who contributed to the GPRD used OXMIS codes for medical events.

GP = general practitioner; **NHS** = National Health Service; **OXMIS** = Oxford Medical Information System; **VAMP** = Value Added Medical Products.

8-weekly cycle. Feedback is provided on the quality of data recording after each collection. On-line data collection is planned. Contributing GPs are using their clinical system software primarily to create an electronic medical record for the purpose of managing their patients and it should be noted that data extraction from their systems for the GPRD is non-interventional.

The data extracted for the GPRD are displayed in table II. The characteristics of GPRD data, their strengths and weaknesses and consequences for pharmacovigilance applications are documented in table III. The validity of Read Clinical Terms used to record medical signs, symptoms and diagnoses is variable. Diseases unfamiliar to the majority of GPs, e.g. ophthalmologic diseases are more likely to be recorded with less accuracy. For formal studies, it is recommended that algorithms are developed to address issues of incomplete data recording, e.g. severity of disease is defined by a combination of drug exposure, dosage instructions and test results, and that an assessment of the specificity and sensitivity of recorded Read terms is estimated from free text entries and/or source data verification via acquisition of anonymised hospital discharge letters, outpatient referral letters, etc. Well conducted studies require an understanding of the UK health system as well as epidemiological principles.

Table III. Characteristics of General Practice Research Database (GPRD) data

Characteristic	Implications for pharmacovigilance	
	strength	limitation
Observational population-based data collected post-marketing – drug exposure and health effects are collected prospectively in an unbiased manner from 'cradle to grave' population[a] in primary care	Enables assessment of population at risk, drug usage pattern (actual vs licensed indication and dose) and assessment of benefit and risk in normal clinical practice i.e. in populations not studied in clinical trials – different age and gender distribution; patients with multiple medications and co-morbidities Enables comparison of drug risks with treatment alternatives not studied in clinical trials	Confounding by indication: drug treatment may depend on severity of underlying disease. Markers of severity of underlying disease are often not recorded and comparison with alternative treatment strategies may yield confounded results. This is a problem when outcome to be studied is associated with severity of indication for drug use
Large size (3 million active patients, over 35 million patient-years), with several years of longitudinal continuous data recording	Enables rare outcomes (incidence rate of less than one per 10 000) which could be undetectable in clinical trials to be studied in a population with well-defined demographics, exposure duration and observational period. Enables outcomes with longer latency period to detected. Able to study natural history of disease and its frequency. Enables estimation of attributable and relative risk	Depends on licensing and marketing status, frequency of drug exposure and outcomes in GPRD. Despite large size, only limited data are available for newly marketed drugs, particularly those with slow market penetration Disease and exposure information in non-GP community settings, e.g. family planning and genito-urinary medicines clinics is incomplete. In hospital tests, drug exposure and length of stay are not recorded in GPRD. Discharge diagnoses are, however, recorded routinely in the patient's electronic record. Does not include complete over-the-counter or herbal medication information. Only allows study of prescribed medicine, which is used as a proxy for dispensed or consumed medication
Comprehensiveness, completeness and quality of data, including access to follow-up service at practice for verification for outcome validation and abstraction of additional information	Enables validation of medical outcomes Enables development of operational algorithm for uniform outcome definition	Screening tests not routinely performed or performed outside the GP practice may not be recorded. Outcomes correspond to clinical manifestation or detected disease and may not be fully recorded. Varying quality of information on clinical outcomes
Data available in online database	No need for *de novo* collection – for cohort, case-control and 'nested' case control studies. Allows rapid access to study emerging issues. Enables acquisition of additional data for decision making particularly important for resolution of issues with high public health impact	Role of chance findings, confounding and potential biases may restrict inference from study results

a Data on prisoners, members of the Armed Forces, homeless people and people treated by private general practices are not represented in GPRD. These excluded patients comprise a very small percentage of the general population.

GP = general practitioner.

1.2 Data Quality

1.2.1 Data Integrity

A series of data searches are run routinely on receipt of a collection to ensure that any gaps in longitudinal data are detected prior to loading onto the database. In such cases, investigations are initiated to determine the cause and a recollection of data performed. In addition, the monthly recording of referrals, tests, immunisations, repeats, prescriptions, medical records is analysed in order to identify other implausible recording patterns. The integrity of data transfer is also ensured by comparing audit sequence numbers of incoming collections versus the last collection loaded into the database.

1.2.2 Completeness of Data

Data quality is assessed at a patient and on a practice level. For all patients in the Full Feature (FF)-GPRD, a quality flag is generated as a measure of the quality of data recording with a patient being assessed as 'acceptable' if the following criteria are met:

- acceptable registration status, i.e. patient registration status is applied, permanent or transferred out;
- acceptable event recording, i.e. no records are recorded prior to the patient's year of birth;
- acceptable recorded age, i.e. patient is less than 115 years;
- acceptably recorded gender, i.e. male, female or indeterminate, as defined by the patient gender flag, and have valid data according to all of the previous criteria.

1.2.3 Practice-Related Data Quality Measures

A total of ten practice-based measures are applied to derive the practice up-to-standard (UTS) date. The UTS date includes the percentage of 'acceptable' patients, the monthly prescription rate, percentage of prescriptions with a medical indication, death rates and recording of cause of death, outcome of pregnancy, referral rate and percentage of referrals with a recorded clinical speciality. The UTS date is assessed for each practice and defines the first date at which an individual practice's longitudinal data met the GPRD-defined minimum standards for data recording quality[21] and are suitable for general research purposes. Ninety-five percent of practices available via the FF-GPRD meet the UTS requirements.

1.3 Recent Developments

The GPRD data with which most researchers are familiar were collected from practice software called VAMP Medical (VM). In 1995, a new Windows-based clinical system software called Vision was introduced. Many contributing practices upgraded to use this software in subsequent years and more were recruited. All current contributors to the database use this software in their practice.

The Vision clinical system software provides much improved clinical functionality over VM and is accommodated by a very different underlying computer coding and table structure. A unique consultation identifier links all entries recorded at the same consultation. Data capture is richer and more highly structured, e.g. structured data areas are used to record details related to topics such as pregnancy, contraception, drug toxicity, lifestyle factors, and a variety of diseases including asthma and diabetes mellitus. Quantitative as well as qualitative results of tests are now available, including the normal range for the laboratory conducting the tests.

The software of the original GPRD was unsuitable for validating data received in the Vision format and could not accommodate the new format data. The MCA invested over £3 million in developing a new database, which has become known as the Full Feature GPRD, to enable legacy data and new data from practices using Vision software to be validated and aggregated, stored in a technical architecture designed to support flexible and efficient querying and accessed on-line for the first time.

1.4 Data Access

Access to the data is provided under licence from the MHRA. Protocols for studies or research the results of which are to be published or communicated to third parties requires prior approval from the GPRD Scientific and Ethical Advisory Group (SEAG). Further information on SEAG's Terms of

Reference is available at http://www.gprd.com/html/index.asp?main = seag.htm. Conditions for use of the data are standard for all users, including the MHRA's Post-Licensing Division.

New data access options have been introduced by the GPRD Division, which is the only source of updated GPRD data. Details of services and fees are available on the GPRD website (www.gprd.com). The MHRA has reduced the licence fee for full access to the database by over 40% since taking on responsibility for the GPRD and has introduced academic rates for non-commercially funded research to support wider academic use of the database.

As well as provision of datasets on CD-ROM, access to the whole or partial data set has been available on-line since the launch of Full Feature GPRD in 2001. Researchers based in Germany, Sweden, Spain, Switzerland, UK and North America are now accessing the database remotely and downloading subsets of data via file transfer protocol (FTP) for further analysis in their preferred statistical/data management software. A range of access levels and data modules are available to enable researchers to customise access according to their research needs.

In addition to the enriched raw data from practices using Vision clinical system software (including generic and proprietary drug names as recorded at the practice) available in the FF-GPRD data warehouse, a number of value-add features have been introduced by the MHRA to support researchers. These include:

- mapping of the original Read Clinical Term to the Medical Dictionary for Regulatory Activities (MedDRA) terminology and mapping of the Multilex drug/product name to the hierarchical GPRD Drug/Product Dictionary [which incorporates the Anatomical, Therapeutic, Chemical (ATC) and British National Formulary (BNF) classifications] to support flexible and comprehensive data retrieval;
- data quality markers at the practice and patient levels (Practice UTS date and Acceptable Patient flag, respectively);
- the facility to run patient profiles which present patient registration details, medical, prescription, test, referral, repeat and immunisation data chronologically;
- tools to support efficient data extraction and formation of study cohorts, e.g. random sampling and matching;
- tools to support analysis in formal studies (person-time calculation);
- a tool which converts dosage free text into daily dose;[22]
- a mother-baby link[23] which is based on a family number (rather than the common household number which has been used historically), pregnancy outcomes and registration details of newborns;
- access to socio-economic data at the practice level.[24] In future, patient level data will become available.

2. Use in Signal Evaluation

The use of pharmacoepidemiology in pharmacovigilance, particularly in the evaluation of signals identified via spontaneous reporting schemes and the literature has been reviewed elsewhere[25-27] as has the specific use of the GPRD for pharmacoepidemiology.[28] The GPRD has been used to study most major drug classes used in primary care and a wide spectrum of clinical outcomes. Typically, data from the GPRD have been used to strengthen or refute signals, to quantify absolute and relative risks and to identify sub-populations at risk. The data have enabled researchers to investigate a wide range of hypotheses by applying a variety of descriptive and analytical study designs including cross-sectional, case-control, cohort, nested case control and case time cross-over.

Results of studies conducted on the GPRD have been used to inform regulatory decisions (see table IV for examples). In many cases, such studies have provided reassurance about the safety of medicines, illustrating the importance of a resource which enables studies to be conducted rapidly (no *de novo* data collection required) to inform regulatory decisions which, by necessity, are made within limited time frames.

Table IV. General Practice Research Database (GPRD) data: examples of use to inform regulatory decision making

Drug	Signal evaluated	Outcome	Reference
Measles, mumps and rubella virus vaccine	Autism	No action needed	29,30
Dexfenfluramine/fenfluramine	Cardiac valves lesions	Drug withdrawal	31
NSAIDs	Upper gastrointestinal bleeding – variation in relative risk between individual drugs	User information to change practice	32
Human insulin	Hypoglycaemia	No action needed	33
Selegiline	Mortality	No action needed	34
Calcium channel blockers	Cancer	No action needed	35
Chloramphenicol eye drops	Aplastic anaemia	No action needed	36

Data for the GPRD are also used to triage safety signals identified through spontaneous reporting schemes by providing ready background incidence rates of diseases and drug exposure (denominator) data.

2.1 Unexploited Applications of the Data

Despite the GPRD's broad usage for pharmacoepidemiology there are several potential applications which have not been exploited widely. These include:

- Assessment of the impact of maternal drug exposure on pregnancy and pregnancy outcomes, neonatal and early childhood health. Counts of drug exposure in pregnancy are displayed in table V (see McKeever et al.,[37] Jick and Ferris[38] and Ruigomez et al.[39] for usage in this field).

Table V. Full Feature General Practice Research Database (GPRD) – examples of drug exposure in pregnancy

Substance	Prescription count (× 1000)
Paracetamol (acetaminophen)	>62
Clotrimazole	>60
Salbutamol (albuterol)	>54
Hydrocortisone	>51
Amoxicillin	>28
Beclomethasone	>22
Codeine	>20
Human insulin	>8
Fluoxetine	>7
Paroxetine	>5
Carbamazepine	>5
Metoclopramide	>5

- Study of medication use in children. This is likely to become an increasingly important data source as plans for licensing of medicines for paediatric use progress.
- Surveillance of medical devices and appliances. The GPRD incorporates prescriptions for all appliances prescribed in primary care, as well as data on patients who have received cardiac valve replacements, pacemakers, intra-uterine contraceptive devices, etc.
- Studying the impact of genetic profile on susceptibility to clinical efficacy and adverse drug reactions. Genetic information is not collected by the GPRD but, subject to ethical approval, could be collected for *ad hoc* studies.
- Provision of evidence of safety in use to support applications for change in legal status of medicines, from Prescription Only to Pharmacy sale or over-the-counter (OTC) sale.

3. Pharmacovigilance Planning

Prospective planning of pharmacovigilance was adopted as an ICH topic (E2E) in September 2002[40] and is likely to become an integral component of the licensing process. It is anticipated that a Pharmacovigilance Specification will be developed to document in a structured manner, the established risks, unidentified risks, potential risks identified in toxicological studies, at risk populations and situations not studied prior to licensing. A Pharmacovigilance Plan will be derived from this. It will document the data relevant to the safety profile of the drug once marketed which will be collected, usually in large populations, and, interestingly, focus on

demonstrating safety as well as identifying harm. It will include consideration of the frequency and clinical course of the treated disease and class adverse drug reactions. For medicines prescribed widely in primary care, the GPRD will provide a rich source of data to inform many components of the Plans. Specifically, it will support analysis of the:

- incidence and prevalence of disease (indication) and its natural history to enable quantitative assessment of outcomes in a reference population;
- incidence and prevalence of concurrent illnesses in the target population, which will often have been excluded from clinical trials;
- drug utilisation in normal clinical practice including: demographics; dose; duration; indication (including off-label); switching and co-medication;
- prospective monitoring of patients identified from clinical trials to be 'at risk';
- outcomes of treatment, including changes in risk over time;
- comparison of event rates between drugs of the same class and those used for the same indication;
- drug effectiveness (benefits in real life setting) enabling clinical impact to be confirmed in target population, hence providing context for an wholistic assessment of benefit/risk.

4. Possible Use in Signal Detection

4.1 Statistical Methodologies

Spontaneous reporting schemes have an impressive track record in identifying signals of drug safety hazards, which have been confirmed using other data sources. Nevertheless, methodologies for signal detection continue to evolve and it is recognised that improvements are required particularly in the areas of drug/drug interactions, syndromes and long latency effects. The most important recent development has been the renaissance in application of statistical methodologies, initially proposed in the late 1960s/early 1970s, to spontaneous reporting databases. These include Proportional Reporting Ratios (PRR) used by the MHRA,[41] empirical Bayes screening used by the US FDA[42] and Bayesian Confidence Propagation Neural Networks used by the WHO Uppsala Monitoring Centre.[43] Recent reviews of these methodologies are available.[44-46]

It is tempting to speculate whether, given the advances in application of data mining techniques used in spontaneous reporting databases and other application domains (e.g. detection of fraud in credit card transactions and nucleotide sequences in gene sequence analysis,[47]) the GPRD could be used for signal detection. The GPRD Division is currently exploring application of techniques such as Gamma Poisson shrinker (GPS) or Multi-Item GPS and simple Poisson models.[48]

Signal detection has been likened to seeking a needle in a haystack.[49] Although the challenge may be greater in the GPRD than in spontaneous adverse drug-reaction (ADR) databases since it is not a database of aggregated clinician-defined possible drug reaction pairs, the GPRD includes denominator information. Furthermore, clinical outcomes, signs and symptoms are routinely recorded in the GPRD without the suspicion of an adverse reaction, hence providing a pool of unbiased and comprehensive information. Observed incidence rates of predefined clinical outcomes with drug exposure can be derived from the GPRD and compared with background rates of these clinical outcomes, taking into account the temporal association between clinical outcomes and drug use in the context of the aetiology and natural history of the disease. Stratification by age, gender and duration of drug use could become part of the routine analysis.

In some quarters data mining has acquired a derogatory connotation and been referred to as data 'dredging', 'snooping' or 'fishing'.[48,50] Rigourous criticism of query protocols and interpretation is of course required. Since data mining a large dataset like the GPRD may generate thousands of possible associations, it would be essential to ensure that the outcome of its application in this field was not expenditure of considerable resource investigating 'noise' with little demonstrable benefit in public health[51] or alternatively, reticence at acting when it is known that the system might produce signals as a

result of chance.[52] The number of false positives could be reduced by adjusting for multiple testing.[53,54]

In conclusion, data mining for drug safety hazards in large epidemiological databases such as the GPRD is experimental at present but may be an additional tool in signal detection, particularly for drug/drug interactions and long latency effects. Of course, signal detection and evaluation should not be conducted in the same study population and some experts argue that the GPRD should be reserved for signal evaluation.

4.2 Novel Source of 'Spontaneous' Suspected Adverse Drug Reactions

The Vision GP clinical system software from which data for the GPRD are now extracted incorporates a "Drug Allergy and Intolerance Structured Data Area" which prompts GPs to record a diagnosis or symptom when an adverse reaction to a drug, immunisation or device is suspected. It also enables the GP to assign a severity rating (minimal, mild, moderate, severe, very severe, fatal) and a certainty assessment (tentative, unlikely, possible, likely, certain, absolute). To date this facility has been used at least once by 95% of contributing practices currently loaded in the FF-GPRD data warehouse and the number of records has been increasing steadily from around 700 in 1995 to almost 25 000 in 2001.[55]

This may constitute an important new source of 'spontaneous' ADRs for use in signal detection or for signal confirmation. The advantage over traditional spontaneous reporting schemes is that it includes denominator data and the full past history of patients. Hence, it can be used to estimate the incidence rate, excess risk and relative risk of suspected ADRs with adjustments for age, gender, dose, duration of treatment, concomitant medication and previous history. However, coverage of a base population of three million (compared with the whole UK population) will restrict its utility particularly for very rare events.

5. Possible Use in Assessing the Impact of Pharmacovigilance and Regulatory Action

Monitoring the impact of interventions arising from pharmacovigilance is important to ensure that lack of effective implementation can be identified at an early stage and additional action taken as necessary, and to ensure ongoing refinement of processes. Furthermore, increasingly, public sector organisations are required to justify the resources deployed in performing their role and medicines regulators are no exception to this. However, developing metrics and outcome measures to demonstrate pharmacovigilance is effective in protecting public health and to quantify the benefit in order to answer a Health Minister's question of "How many lives have been saved as a result of pharmacovigilance this year" is not easy. It is a problem encountered with other public health interventions.[56]

It has been routine practice for the MHRA's Post Licensing Division to observe the impact of interventions on spontaneous ADR reporting, whilst accepting this is subject to bias,[1] and to use data from a variety of sources, including the GPRD, to conduct time trend analyses on the impact on drug utilisation e.g. dosage, co-medication and contraindications. It is recognised that changes in prescribing behaviour provide a useful surrogate outcome measure, but a truer outcome measure of the public health impact of interventions would be assessment of morbidity and mortality. The MHRA is planning to assess the utility of GPRD for this purpose for drugs prescribed in primary care. Impact assessments will need to be designed carefully to enable any failures in the communication process[57] to be distinguished from the impact of changes in prescribing. In the case of drug withdrawals, the potential negative impact on previously well controlled patients who have to change medication must also be taken into account.

6. Conclusion

The implementation of risk management strategies and pharmacovigilance plans coupled with earlier access to medicines through conditional approv-

als will require the wider application of epidemiology to post-marketing surveillance and has been described as "a call to arms for pharmacoepidemiology".[58] One commentator speculated that in the future a pharmacovigilance team "will not be a stand alone department responsible for monitoring drug safety, but a global centre of knowledge intrinsic to the research and development operation as a whole".[59]

As the focus of pharmacovigilance broadens to include more explicit consideration of 'what diseases do to patients' as well as 'what drugs do to patients', the value of databases such as the GPRD which provide comprehensive, high quality longitudinal patient records will increase. Forty years after the thalidomide tragedy, a wholistic approach to pharmacovigilance is emerging and 'pharmacovigilantes' may reflect on whether the discipline of pharmacovigilance is coming of age.

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