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ABPI eHealth and health information

Requirements update
July 2013

Purpose: To provide an ABPI member and industry perspective on the service levels required for the UK to remain a location for research based on routinely collected health and other related data.

Intended audiences: Health & Social Care Information Centre (HSCIC), Clinical Practice Research Datalink (CPRD) and other data provision services; and the pharmaceutical industry.

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Background

The original ABPI document 'Industry requirements for eHealth research in the UK' published in 2010 (see Appendix 1) sets out the main requirements envisaged by representatives of the pharmaceutical industry. Much of the document still stands, however we have seen a number of developments since that time which need to be acknowledged; and new goals have emerged accordingly. During discussions about updating the requirements, it became clear that there is still much work to be done before the priorities and concerns, for industry to benefit from greater availability of data and systems at a practical level, are widely addressed.

The December 2011 launch of the Government's 10-year Strategy for UK life sciences led to the announcement of a number of investments and initiatives to build capabilities for research based on electronic health record systems. Important developments have included: the establishment of the Clinical Practice Research Datalink (CPRD); the enhanced role of the Health and Social Care Information Centre (HSCIC) and the recent launch of the eHealth Informatics Research Centres (eHIRCs).

The CPRD will focus on delivering data and services to NHS, academic and industry customers whilst the HSCIC will co-ordinate the acquisition and linkages of the different data sources, and manage the underlying coding. The HSCIC already provides some 293 data sets either directly or indirectly, with more available through the NHS Business Services Authority. The eHIRCs were formally launched on 1 May 2013 and more detail on their roles will become available in the following months.

The items discussed below reflect the desire to support data provision services and to ensure that the UK's health information & data, and services, becomes widely adopted and valued. These service requirements are intended to support these bodies and industry consumers in planning for the future and to ensure that adoption of UK health information & data becomes routine. We recognise the potential for the broad range of information that is being evaluated but would like to encourage consideration of the priorities listed below as directly affecting the pharmaceutical industry's adoption of the main data sets and hence the capacity to attract research investment to the UK in an increasingly competitive world.

This list of requirements has been compiled from experience of working within the life sciences industry with an international perspective, and is intended to provide an insight into the way decision makers in those organisations allocate their resources (for example – regarding whether to choose country A or country B for a retrospective data study). It is hoped that this will be useful to any organisation hoping to engage in collaborative research with such a company. The key actions that need to be undertaken to establish a competitive health information and data informatics service in the UK which will serve the life sciences industry effectively into the future are:

1. Provide information about quality and validation of data
2. Provide a clear plan for accumulation of additional data
3. Provide information about the interfaces between databases of regional providers
4. Provide information that enables assessment of a medicine's success in meeting healthcare needs by reviewing data derived from its usage
5. Provide consistent and transparent rules for licensing data
6. Promote the benefits of research based on routinely collected health care data
7. Provide support for alternative data models and coding systems
8. Establish a clear service model and associated service levels.

We have also been asked to address the issue of stratified medicine. This requires an in-depth analysis with experts in stratified medicine within the life sciences industry and some relevant considerations for this analysis are set out in the 'Applications' section below and a separate paper is envisaged in due course that reflects this analysis and discussions.

1. Provide information about quality and validation of data

From an international perspective, the number of Real World observational and health information databases is increasing significantly. This gives ever increasing choice in the selection of databases for analysis. Consequently whether a specific database is appropriate for a specific study hypothesis becomes a question of priority for the service provider and the customer.

Ensuring that data is of the highest quality, and that its strengths and limitations are explicit, is critical to ensuring the credibility and maximising the usefulness of any given database. Provision of an assessment of the quality of the general and specific aspects of a database (eg endpoint validation) is vital to ensure the credibility of studies. Additionally, transparency about data collection and conversions will be critical for effective use by third parties. We also believe that a clear, publicly available and detailed description of what is contained within a dataset and what can be achieved with it is vitally important.

It is particularly important that data and service providers give clear evidence of quality to enable international comparisons to be made. Customers would also value clear strategy from providers regarding selection of standards or principles for such comparative assessments to be made.

2. Provide a clear plan for accumulation of additional data

There should be a clearly specified metadata library for the data sources which are currently available, and a clear plan which states when new data sources will become available with projected time lines. There should be a simple mechanism for customers to request new sources. Where affirmative, a planned delivery of the data should be announced. Current examples of new data might be primary care electronic medical records (eMRs; also referred to as electronic health records or eHRs, to encompass all health data and linkages) from systems not covered by CPRD and other providers, Yellow Card Scheme data, hospital prescribing data and biological data. There should be dedicated semantic support for each new data source, able to tell the 'data story' to facilitate correct interpretation by the customer.

3. Provide information about the interfaces between databases of regional providers

Where a federation of regions exists (for example, England, Scotland, Wales and Northern Ireland within the United Kingdom) the service provider should specify the area of jurisdiction. They should ensure that the effect of cross-border use of healthcare is understood, measured, and reported. Where there is a multiple data schema within the jurisdiction, this should be documented and the effect on data semantics reported. Any plans for inclusion of extension or contraction of the jurisdiction of the service provider should be clearly reported.

4. Provide information that enables assessment of a medicine's success in meeting healthcare needs by reviewing data derived from its usage

Although not mentioned in the ABPI 'Industry requirements for eHealth research in the UK'[1] such intelligence should be recognised as a valid non-promotional research activity (for example – measuring prescribing for a newly launched product in a particular patient subgroup) to allow the sponsor to manage internal resources. Part of this process will often be scaling up sample figures to population figures and the service provider should provide validated and documented support for this calculation.

Where information could be of value to healthcare providers or commissioners, there should be a process for consented identification of these groups, to enable such collaboration to occur. This would extend naturally to the identification of healthcare institutions for clinical trial recruitment with well-defined transparent processes, recognising the need to put appropriate safeguards in place.

5. Provide consistent and transparent rules for licensing data

Cost and complexity of current licensing procedures for databases are likely to limit the number of users and hence the ability for a broader research base. We would like to see a single charging schema and single licence for the use of all NHS data. Additionally each data source needs a clear description of the ethics process and associated timelines. This would enable potential users to make an informed decision on which source to use.

The goal of having the gold standard in evidence based data, and the benefit it can bestow on the patients it comes from, will be enhanced by having innovative uses and applications developed by the broader research and medical informatics community.

We would be supportive of consultation on a review of the potential applications, licensing opportunities and methodologies for ensuring appropriate use in both the research and clinical communities.

1. See Appendix 1: Industry requirements for eHealth research in the UK, December 2010.

6. Promote the benefits of research based on routinely collected health care data

The analysis of anonymised electronic medical record (eMR) data by the research and medical informatics communities may have far reaching effects on the understanding of disease, treatments and outcomes (see All Party Parliamentary Group on Medical Research, Summer Reception[2] for a comprehensive assessment of existing projects). However, patients and other groups are cautious about the implications of this development. Understanding both the reasons for this caution, sharing information on the potential for research; and finding a satisfactory framework for enabling the data usage, are critical in promoting the benefits of such research.

The value of the data being collated by the HSCIC and CPRD lies in the insights, abstractions and hypotheses that can be deduced from it. For over three decades most eMRs have not been used efficiently with only local access by primary care physicians. Few tools have been developed that can extract significant meaning.

This is changing as national initiatives that link primary care, hospital, pharmacy and other registries are emerging. In effect patients are contributing to the total medical knowledge, will benefit personally; and provide a lasting legacy to future generations. With this in mind, positive case studies showing the value of linking data to the healthcare system, should be promoted to the public – along with the processes and methods used to generate knowledge based on evidence. One activity that would prove highly effective in encouraging public support would be the use of such data in clinical settings where patients benefit individually rather than use of eMRs being seen solely as the purview of academics, institutions and the life sciences industry.

Achieving validated clinical applications may take some time but the intentions could be promoted in a sustained programme of communication to inform patients and healthcare professionals of the value of the project. Active involvement of the medical profession would also be beneficial, as they have the daily contact with patients. This may be a fruitful area for industry to engage in.

Whilst confidentiality is a significant factor, it is also a potential barrier if not dealt with proportionately. Patients must be included in the communication programme as their support can be enabling and could generate solutions that validate eMR availability further.

7. Provide support for alternative data models and coding systems

The increased need to be able to conduct rapid analyses effectively across multiple data sets also emphasises the potential role of standardised data structures to facilitate such analyses. While there will be a need to preserve the unique aspects of given databases in their own unique data models and data structures, increasingly it will be valuable to provide the data set in a standardised format with minimal information loss and appropriate documentation to facilitate analyses across multiple databases.

With the greater availability of multiple new databases comes the opportunity for analyses (at least feasibility analyses) to be conducted across multiple databases from different regions quickly and effectively. However, many databases use different coding schemes that lack harmonisation (eg READ, ICD9-CM, Snomed CT, Meddra etc) and mapping on a study by study basis is time consuming, inefficient and reduces confidence of valid comparison between different studies. Standardised, validated and accepted mapping between terminologies would be extremely useful in increasing the amount and effectiveness of work using Real World and other data. Ensuring the quality of the coding as well as the mapping as part of a routine continual process will be increasingly important.

Extending harmonisation into the use of a single standardised database format, a so-called 'Common Data Model', for multiple databases could bring significant advantages and should be explored as a priority, although judicious consideration is needed particularly with respect to the risk of reduced transparency and potential information loss in conversions.

8. Establish a clear service model and associated service levels

The service model (whether it includes software, analytical services, data linkage, hosting etc) should be fully described and provided by staff with appropriate training and skills. The data provision organisation should, from the outset of a customer relationship, manage the expectations of the customer with respect to the service levels

2. All-Party Parliamentary Group on Medical Research - Summer Reception, 2012. Available at: www.acmedsci.ac.uk/download.php?file=/images/publication/APPGMRPr.pdf

that can be expected (for example – regarding query response times or the approach to incident support) and accountability for meeting targets.

A competitive data analytics market is desirable. If the data owners are the only providers of analysis, their fees are typically very high and those wishing to answer a given research question are often deterred from exploring this as a result (especially if they do not have the in-house expertise to analyse the data). Currently identifying alternative data analysts is challenging and their quality is variable.

Applications

During the course of this review we considered the role of eMRs in the evolution and deployment of services to deliver personalised or Stratified Medicine.

Much of what has previously been communicated with the Department of Health has revolved around observational research in the assessment of safety and efficacy of medicines and procedures. These factors will strongly influence industry R&D, payer choice and patient preference.

Stratified medicine in the sense employed here is defined as:

> *"The tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not."*
> ABPI White Paper – 2009

The role of the electronic health record in stratified medicine will be significant and the implications of the following need to be considered:

a) Using existing data from eMRs to assess the statistical probability of optimal treatment given basic phenotype data.
b) Identifying emerging requirements for genotype data such as individual biomarkers; how are these captured and used in clinical settings.
c) Planning the evolution of clinical systems to accommodate and utilise this data.
d) Analytics required to assess and evaluate outcomes based on stratified medicine.
e) Effective access and use of Stratified Medicine, clinician communications.
f) Identifying skills and training to develop expertise in the range of stratified medicine functions.

Conclusion

The UK is already an attractive place to conduct research where access to 'cradle to grave' eMR data and systems is required, with its advantages in terms of availability of data, health informatics skills, and a thriving scientific sector. As a result of the investments being made under the Government's 10-year Strategy for UK life sciences, the UK can maintain and strengthen its position as a country of choice for such research in the future. In order for the potential to be realised, however, there are many practical challenges to overcome. Defining and offering services outlined above, and then meeting service requirements, form just one, but important aspect of these challenges, if the UK is to be relied upon in an increasingly competitive world.

ABPI Pharmaceutical industry Health Information Group (PHIG)
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Appendix 1

Industry requirements for eHealth research in the UK

The UK is on the threshold of a step change in the availability of patient-level data for scientific and medical research. Already a country of choice for researchers who rely on patient databases that have been developed over the past 20 years, the UK is poised to become more attractive with the progress being made by the Government's Research Capability Programme. Central to the success of the Programme will be the effectiveness of the proposed Health Research Support Service (HRSS) in facilitating a wide range of research activities undertaken by the life sciences industry.

If the UK retains and develops expertise in eHealth research, more innovative medicines will be developed; the capital brought into the UK to invest in this type of research will be beneficial to the economy; and UK patients will benefit from better health care.

The purpose of this paper is to develop clarity on the service that the HRSS must provide to the UK life sciences industry for this country to retain its position as a world leader in eHealth research. This paper will focus firstly on general principles and then specifically on the three areas of:

a. clinical trials – feasibility, recruitment and management
b. pharmacovigilance
c. outcomes research.

Although not covered in this paper, personalised medicine[1] has particular significance for the UK as it could offer an area where this country could be uniquely competitive, show international leadership and create a more conducive environment for novel drug and diagnostic R&D. Electronic health records are becoming more established in parts of the UK and this is a critical foundation stone for personalised medicine and will allow genomic and clinical data to be integrated into practice. This will be strengthened further with the implementation of the HRSS, creating a single network of clinical information facilitating both clinical care and biomedical research.

The service – our approach

As part of identifying key features that industry would ask the HRSS service to provide we have approached each of the three topics in the following way:

- Taken note of a recent survey of ABPI members on the HRSS pilot projects and recorded which of the research methodologies and questions were considered to be most helpful to the pharma industry in the UK and why.
- Considered how that research would currently be conducted including details on timelines, different databases and "languages" used, time delays etc.
- Reviewed approaches to eHealth research elsewhere in the world – eg the Observational Medical Outcomes Partnership (OMOP) and Innovative Medicines Initiative (IMI) including clarity on structures to be adopted and security of patient data methodology.
- Described what sort of functionality HRSS needs to provide to industry researchers that would remove or improve current difficulties and provide a competitive service.

General principles applicable to clinical trials, pharmacovigilance and outcomes research

Robustly linked HRSS component databases: As part of the development and ongoing operation of the HRSS, robust linkages between primary care databases, secondary care databases and registries; and specialised datasets will need to be established. In an ideal scenario, the linkage process would involve:

- Development of compatible data fields or a conversion program to allow data from the different sources to be merged, Health Level 7 (HL7) considerations may help here[2].
- Detailed work on coding terminology used for each source, either aligning on one terminology for all sources or developing mapping programs to allow the data to be merged if necessary. It is also important to consider the use of standardised data entry fields in future.

1. Personalised medicine: "the tailoring of medical treatment to the individual characteristics of each patient". The ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not". Critically, it also involves the development, validation and use of companion diagnostics to achieve the best outcomes in the management of a patient's disease or their predisposition. See the ABPI White Paper – The Stratification of Disease for Personalised Medicines: April 16, 2009.
2. Health Level Seven International website. Available at: www.hl7.org/about/index.cfm

- Development of standard search criteria to define key disease areas validated by international bodies and accepted by Regulatory Agencies like the Medicines and Healthcare products Regulatory Agency (MHRA).
- HRSS development complementary with the e-health methodologies being developed, at the Innovative Medicines Initiative (IMI), in the US, across the International Conference on Harmonisation (ICH) region and worldwide
- The ability to query free text fields from individual patient records and electronically key word search (after anonymisation and/or removal of sensitive data).
- Appropriate data protection, consistent for all data sources. Large online databases containing personal information are routinely used in other sectors eg the fields of banking and insurance and similar progress must be made in the area of public health.

Improved General Practice (GP) coverage: The commonly used UK Primary Care Databases (PCD) – General Practice Research Database (GPRD) and The Health Improvement Network (THIN) – cover just 5-10% of the UK population, which limits their usefulness in epidemiology studies, eg the analysis of rarer signals; in economic studies, eg estimating the burden of illness; and in recruitment for trials. Collaboration between PCD providers (IMS, MHRA and Epic) and primary care software providers like Egton Medical Information Systems Ltd (EMIS) which cover over 59% of GP practices in England (52.5 % across the UK) could increase PCD coverage tenfold, greatly increasing the power of studies that can be conducted in the medium term. Implementation of the General Practice Extraction Service (GPES) could raise UK PCD coverage to almost 100% in future.
The expanded pool of data described would greatly increase the versatility of the HRSS and its range of applications: safety data analysis, clinical trial recruitment etc, and would enhance the robustness of results. This would enable more rapid and decisive analysis with great benefits to patient health. The development of the HRSS would create a world leading UK resource and associated skill set that could be marketed globally.

Access to HRSS: All HRSS functionality must be available to the researcher (academic, government or industry funded) at a single access point online for simple queries, with suitable advice and timelines for delivery for more complex queries. The data must also be kept as up to date as possible. A single access point is needed because of the tight timelines[3] needed to analyse safety signals and because frequent interrogation of the data will be required due to the wide range of applications. This method works well for similar service providers such as Lincoln Technologies for the large adverse event (AE) databases (AERS/Vigibase) and the potential high demand for the HRSS, domestic and international, would ensure a significant revenue stream for the service provider.
HRSS has to have a transparent and robust framework for customer engagement and reliability. This should include a clear service agreement with timelines for responses to simple and complex queries, with a transparent fee structure for access and analytic services.

Consistent standards: Consistent standards across all UK databases consolidated to form the HRSS are needed to reduce complexity and to improve interoperability. HL7 standards are being implemented in:

- The message specifications of ICH E2B reports in the ICH region (EU, US, Japan and Canada), including upgrading of the EudraVigilance (EV) database.
- The development of messaging and vocabulary standards for AE reporting within the new US National Health Information Infrastructure (NHII).

The development of HRSS would greatly benefit from early collaboration with initiatives such as the IMI project in Europe and the OMOP initiative in the US; to ensure consistency/compatibility.

Scientific advice: As the group who will develop the best understanding of the strengths and weaknesses of the linked data sources, HRSS should offer advice on study design. It will be important for HRSS staff to be trained in and have experience in conducting research using patient level data. This will improve the quality of research undertaken, and increase the proportion of studies approved in formal review.

3. The need for HRSS to be responsive within very limited timescales (ideally hours, days) cannot be overstated. Rapid access to data is required when addressing an emerging safety issue.

a. Clinical trials

The HRSS or any system for delivering eHealth support services to industry should have the capability to provide data of sufficient quality for clinical research.
Three key areas where industry would want to interface with such a service in relation to clinical trials are:

- *protocol optimisation*
- *patient identification/recruitment*
- *trial execution.*

Protocol optimisation
The HRSS should be suitable to provide protocol optimisation information efficiently. The system should allow for a set of eligibility criteria to be entered and estimate likely numbers of patients that match these inclusion/exclusion criteria. The HRSS should also allow inclusion/exclusion parameters to be varied eg by changing age range. Feasibility information could be used to optimise trial design, for example through the impact of modifying inclusion and exclusion criteria on patient populations for the study.

Patient identification/recruitment
The HRSS needs to support and enhance patient recruitment into studies. Since much of the patient characteristics relevant for patient identification – such as diagnosis, age, gender, lab values – are stored electronically, it should be possible to use the service to support patient recruitment.

The service should have the capability to:
- Identify potential sites[4] which have appropriate patients for the study.
- Identify principal investigators in each of the sites identified who could possibly approach and recruit potential participants.
- Identify potential patient participants and enable contact with them by investigators.

Trial execution
Clinical research would be made more efficient by an effective interface between the Case Report Form (CRF)[5] and the HRSS. A two-way passage of information could facilitate a reduction in the administrative burden and duplicative form filling while running a study by:
- A pre-population of the CRF by the HRSS drawn from the data already held on a patients' electronic health record (EHR). For each subsequent visit made by the patient during the study, relevant information entered by the investigator in the EHR could be directly transferred into the CRF.
- Additional information needed by the study could be electronically filled in by the investigator and that information could be populated to both the EHR and the CRF via the HRSS.

This system would require the EHR and electronic CRF used to be compatible and the interchange of information between the two to be possible via the HRSS. Other benefits of this interaction could include electronic long-term follow-up and the ability to request the collection of additional clinical information during a routine patient visit.

Governance
Currently only physicians can assess the suitability of patients for trials and approach them since medical records are confidential and patients' consent is required either for trial participation or for use of identifiable data in EHR for research. Whether an 'opt out' (allowing automatic use of EHR for research unless specifically instructed by the patient to 'opt out') or 'opt in' (specific consent from the patient for record use required) is used, will impact the speed and effectiveness that could be achieved for clinical trials through the HRSS. Clearly from the perspective of efficient research processes an 'opt out' system is preferable, but this would need to be alongside a major education and awareness campaign for the population where knowledge of the methods and benefits of medical research is currently very low. The information governance framework for the HRSS must exceed UK minimum governance standards.

4. In addition to the three key features of patient identification and recruitment and site selection listed here, other considerations in choosing locations for trials are: concurrent trial workload, previous experience in similar clinical trials, recruitment and retention in previous clinical trials, site personnel study experience and training, availability of facilities such as laboratories, availability of trial specific equipment (eg imaging). However it is not anticipated that the HRSS would assist with the need for such information in addition to patient specific information for recruitment purposes.
5. The CRF is the electronic patient documentation used in clinical research and is used by sponsors to collect data from enrolled patients at each participating site.

Overall benefits for clinical trials

An HRSS which is capable of facilitating the three key areas of research detailed would greatly enhance the competitiveness of the UK in the clinical research environment, reducing timelines and improving the quality and exchange of information. The HRSS should streamline current cumbersome processes of trial feasibility, allowing changes in the protocol to be assessed quickly; timely identification of sites and potential investigators; and recruitment of trial participants. The HRSS should ensure that patient EHRs are complete, reflecting key information gathered during and after participation in trials drawn in from the CRF, while ensuring that CRFs are accurate, reflecting information drawn from the EHR at the start of a trial.

Initiatives outside the UK to improve clinical trial capability from linked medical record databases

1. The European public-private IMI project is considering prioritising funding for the development of the use of electronic patient records to underpin better trial recruitment and management along the lines discussed above. Specifically it has described and listed the following attributes of the system it would wish to fund development of:

European Medical Information System

- *Better patient selection for clinical trials based on complete and accurate data including. diagnostic and treatment information*
- *Improved safety through post marketing surveillance*
- *Reduce healthcare cost*
- *Enhancing multiplicity and flexibility in clinical trials*
- *Enrolling studies for rare disease*
- *Potential link to genetic information; Improve ability for patients to join clinical trials*

2. In addition several groups in the US are working to improve clinical trial recruitment and management though better use of patient records. For example

- *The PACER NY pharma/IT industry consortium – a consortium of leading pharmaceutical and information technology companies working to develop an innovative pharmaceutical-clinical research platform for translational medicine, adaptive trial management and follow-on pharmacovigilance, pharmacoeconomic and drug safety sciences. The pace of development is fast and the build and test phase is expected to be complete by 2015.*
- *eCast corporation – 25 sites in eight regions in the US – a data analytics focus but with a clinical trials division whose aims include the use of data to improve protocol design and clinical trial recruitment.*

b. Pharmacovigilance

Current situation

In pharmacovigilance (PV), pharmacoepidemiological (or E-health) tools are most frequently used for evaluation of safety signals, as components of EU Risk Management Plans (EU-RMP) or in Phase IV or post authorisation safety studies (PASS).

At present, the most commonly used tools are primary care databases (PCD) like the General Practice Research Database (GPRD) or The Health Improvement Network (THIN). Prescription event monitoring (PEM) is another frequently used methodology, particularly as part of risk management activities early after product launch.

The tools described above are all UK based but are used across Europe and even globally, as part of risk management or to assess safety issues. There is however, a desperate need for expanded functionality, additional methodologies and larger data sets. The development of the HRSS would link many key UK databases to create a world leading resource for safety surveillance which will address these three key needs going forward.

Routine signal detection and evaluation

HRSS functionality will complement current signal detection methodologies such as data mining in AERS, Vigibase or EudraVigilance[6], literature review or Periodic Safety Update Report (PSUR) production. The key difference would be that the pharmacoepidemiological analysis of a potential signal would be more comprehensive and robust due to the expanded PCD coverage and new linked datasets. For example, PCD only

6. Compatibility with associated tools such as Prosanos CLAERITY needs also to be considered.

contain GP data but adverse events that occur in hospital can be equally important. Robust linkages of PCD with secondary care data (SCD), like Hospital Episode Statistics (HES), accessed via the HRSS, would allow the choice to work with PCD and SCD data combined or separately as appropriate. This creates a more representative sample than presently possible and increases the power and robustness of studies. Consideration must be given to the benefits and feasibility for research of standardised coding[7] and validate results from these studies to ensure they are highly regarded by decision makers, including regulators. Signal evaluation could also be performed by linking specific disease registries to the large power of the primary care databases and secondary care databases. Hospital prescribing is not collected centrally[8]. Consideration should be given to the benefits of central collection and perhaps a linkage with the Health Hospital Pharmacy Audit Index.

Risk management

HRSS functionality should also be used in Phase IV studies and there are clear benefits for current study methods such as PEM and Exposure Event Tracking (ExEtrac), described below in more detail. The tracking possible via the HRSS could even be used to greatly simplify the conduct of extensions to Phase III studies.

- ***electronic Prescription Event Monitoring (ePEM):*** PEM studies are frequently performed soon after product launch, but the methodology is paper based and labour intensive. In PEM, GPs who prescribe a new medicine are asked to report on a 'Green Form', all events recorded in the patients' notes during a specific time-period since the patient started treatment with the medicine. PEM allows identification of AEs that may not have been suspected as due to the drug under surveillance by removing the need for the prescriber to give an opinion on whether an AE was caused by the medicine.

  The development of tools, with appropriate governance, to access the free text fields of electronic medical records as part of the HRSS, coupled with increased PCD coverage, will allow PEM to be performed electronically as a database study, where information is gathered from the free text as well as structured fields of EHR. ePEM would be faster and cheaper and could potentially link with additional sources of data via the HRSS. PEM often covers 40-60% of the UK population however so expansion of the current PCDs is the first step required to develop this methodology.

- ***Exposure-event tracking:*** Exposure-event tracking by GPRD (ExEtrac) uses software to track an exposure to a medicine/vaccine and a particular AE from primary care notes but is currently limited by the size of UK PCD. As above, expansion of PCD coverage (via partnerships/GPES) and the linking of PCD and SCD etc. is essential if we are to make this tool a world leading resource. The ability to track AE in close to real time, from a range of sources (PCD, SCD and registries) via a single HRSS query tool, will be a powerful and cost effective addition to the safety surveillance toolkit for when close surveillance of a medicinal product is needed.

- ***Phase III clinical trial extensions:*** HRSS functionality could even be used to conduct cheaper extensions to Phase III clinical trials to examine safety outcomes. Patients enrolled in a clinical trial could be tracked via the HRSS in the open label extension phase, which would link to the patients' EHR and automatically update at pre-specified time periods.

Developments such as these can not take place however, without significant investment in UK IT infrastructure.

Overall benefits for pharmacovigilance:

The greatest benefit of the HRSS would be a step change in the management of drug safety in the UK and the generation of a world leading system and skill set. Rarer signals could be evaluated and more common signals could be analysed with greater robustness. This improved functionality will allow MAH and Regulatory Agencies to more quickly decide if a safety issue is real and to more rapidly inform patients as a result.

7. HES coding is currently for the purpose of charging and commissioning within NHS, not for research purposes.
8. There is no central NHS collation of information on medicines used and issued in NHS hospitals similar to that in primary care. The Prescribing Support Unit has, however, access to the Health Hospital Pharmacy Audit Index (HPAI) database. Data is collected and collated, on a commercial basis, by IMS Health (Intercontinental Medical Statistics) and made available to The NHS Information Centre under a commercial contract.
   The HPAI is based on issues of medicines recorded on hospital pharmacy systems. Issues refer to all medicines supplied from hospital pharmacies: to wards, departments, clinics, theatres, satellite sites and to patients in out-patient clinics and on discharge. Therefore, the HPAI monitors usage levels by hospitals rather than purchases by trusts which may be acting for a consortium of trusts. This avoids bias introduced by hospitals redistributing medicines after purchase.
   Costs are calculated by IMS Health using the Drug Tariff and other standard price lists. The coverage of hospitals is not complete, although 97 per cent of acute NHS beds across England are included.
   The PSU publishes a national report, based on this data each year.

Risk management has become standard practice in pharmacovigilance and the use of Phase IV/PASS studies is increasing. The HRSS will enable the development of novel risk management methodologies like ePEM, large linked database exposure event tracking and cheaper follow up of Phase III study extensions.
The HRSS is an IT resource that is much cheaper than conventional interventional methodologies to operate and will enable significant additional savings through improved patient protection.

Initiatives outside the UK to improve pharmacovigilance from linked databases:

1. The OMOP initiative in the US was established to inform the appropriate use of observational healthcare databases for active surveillance by:
   - *Conducting methodological research* to empirically evaluate the performance of alternative methods on their ability to identify true drug safety issues.
   - *Developing tools and capabilities* for transforming, characterising, and analysing disparate data sources.
   - *Establishing a shared resource* so that the broader research community can collaboratively advance the science.

   The OMOP partnership has developed, through the use of a common data platform, a range of methods to improve surveillance of safety signals appearing across disparate patient record databases. A recent publication[9] describes the transparent, open innovation approach designed to systematically and empirically study critical governance, data resource, and methodological issues and their interrelationships to establish a viable national program of active drug safety surveillance using observational data. The article describes the governance structure, data-access model, methods-testing approach, and technology development of this effort, as well as the work that has been initiated.

   In parallel to the OMOP initiative, the Food and Drug Administration has established *Sentinel* – a network of distributed observational databases (administrative claims and electronic health records) to monitor the effects of medicines post-approval for safety purposes. The aim is to have linked databases and be able to retrieve information from 100,000,000 patient records by July 2012.

2. As noted above one of the aims of an IMI 'European Medical Information System' would be to improve safety through post marketing surveillance.

c. Outcomes research and epidemiology

The UK has long been considered a leader in outcomes research and epidemiology due to the NHS providing 'cradle to grave' healthcare, and the availability of large primary care datasets. A wide range of studies can be performed with the data, such as outcomes research studies assessing the relative effectiveness of treatments; economic studies evaluating the burden of disease or costs of treatment; and pharmaco-epidemiology studies exploring the use and impact of drug treatments. More recently the growth in linkages between GPRD, Health Episode Statistics and registries that has taken place in parallel with the planning phase of HRSS has given some indication of what advantages a national linked dataset would offer. The success of HRSS in building on this foundation will depend on a number of factors;

The breadth, depth and quality of linked datasets

- The linked data from primary care must include the majority of English practices to enable outcomes studies in recently licensed medicines and in rare conditions.
- HRSS should maintain a flexible approach to the timely inclusion of additional datasets where they are of sufficient quality. The addition of prescribing information from secondary care sources, including outpatients, should be considered a priority from a research perspective.
- It should provide feedback to data providers on the quality of data submitted, and include quality indicators on all data for researchers to assess whether it is suitable for their own project.
- Ability to follow patients longitudinally over an extended period is crucial. Tools should be provided (eg accurate registration dates) that allow researchers to follow a patient between different localities without duplication of events. This could be performed via a unique patient identifier, subject to appropriate governance.

9. 'Advancing the Science for Active Surveillance: Rationale and Design for the Observational Medical Outcomes Partnership' in Annals of Internal Medicine. *Ann Intern Med November 2, 2010 153:600-606.*

Timely access to linked data

- Ability to conduct feasibility studies quickly and easily, preferably via an online tool which can inform on numbers of patients and datasets available.
- Transparent and rapid approval process for research protocols. Sequential review across multiple database owners may cause significant delays, particularly where smaller database owners have infrequent review meetings.
- Where feasible, broad approval for types of research using linked databases and the methodologies adopted in making the linkages should be in place. Individual research requests would then only require a review of the scientific merits of the proposed study rather than repeating the review of the databases used and the linkage mechanisms which is a lengthier process and leads to delays which would appear to be unnecessary.

Access to additional data

- Free text may contain data necessary to assess outcomes not formally coded (eg minor symptoms, quality of life). It should be available either directly (anonymised) or via automatic queries.
- The HRSS should provide a clear process for the validation of events detected in the EHR with the recording physician. Facility to include Patient Reported Outcomes (eg Quality of Life questionnaires) should be considered.

Initiatives outside the UK to improve outcomes research from linked databases

The objectives of the initiatives outside the UK relating to improving trials recruitment and pharmacovigilance will also underpin improved capability in outcomes research.

Conclusion

We support the development of the HRSS and recognise its importance to industry in conducting clinical trials, pharmacovigilance and outcomes research. It will also have the knock-on effect of generating inward investment that will be boost the UK economy. The ABPI will continue to provide input and support as HRSS develops, with a view to making this tool the best possible resource for this country.

ABPI eHealth Research Group
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Association of the British Pharmaceutical Industry
7th Floor, Southside, 105 Victoria Street, London SW1E 6QT
t +44 (0)870 890 4333 abpi@abpi.org.uk