

Review of UK Health Research

Response from

**The General Practice Research Database
(GPRD) Group**

at the

MHRA

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Prepared by

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This response is in two parts:

Part 1. General comments not specifically addressed by the questions (Annex B) but which were covered in the presentation made to the Cooksey team (17/07/2006)

Part 2. Answers to the Annex B questions.

Part 1. General comments

1. Data richness is the key

In bringing medicines and technologies, using the UK as a key research centre, to market
.....and in ensuring patients get best treatments.....
.....and that the health service gets value for money....
.....and as a consequence there is UK health....
.....and wealth

...the .Pharmaceutical industry cannot be too data rich

The UK health data bank, as exemplified by GPRD, is already one of the richest in the world.....

....upon which to build, now, as a platform for that which SUS (Secondary Uses Service) can additionally deliver....

....and in so doing reap early, earlier rewards in both health and wealth

2. Available now, use now, build on via SUS for later

Other countries are already building their own new health IT system as well as data banks and biobanks.

What they do not have is, as with GPRD, the historical data, the history of its use and the experience, to be major players, now.

3. Maximise and extend the existing links between the Pharmaceutical Industry and GPRD with regard to the availability of UK/NHS data. Additionally bring together the different data groups (1) Clinical Trials and (2) Epidemiology/pharmacoepidemiology (Drug safety, outcomes, risk management, economics, biogenetics/genomics).

The GPRD group already has extensive links with global Pharma via their departments associated with drug safety, outcomes, economics and risk management. The NHS and academic centres have equivalent contacts with the clinical trial departments. A synergistic effort would be of benefit.

4. Incentivise additional UK based pharmaceutical research by enabling and promoting methodologies that the UK system of healthcare delivery / existing and developing IT systems can uniquely enable or, where there is an established lead.

Phase 4 randomised database studies (PROBED) (see page 7 for more details) are essentially a methodology for which the UK system of healthcare delivery and existing and future IT system are ideal. These studies can play a major part in rapidly ensuring that medicines available in the UK and elsewhere are safe and effective in real world use.

The GPRD group has also, been researching a new methodology to more rapidly predict the risk benefit profile of new medications (see page 6 for more details). Such a methodology requires access to a significant volume person specific healthcare data that can be enabled by the SUS.

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Part 2

Cooksey Review Questions	Response	Background/supporting information
<p>2. a) <i>What do you believe are the key scientific challenges facing health research, in the UK over the next decade?</i></p> <p><u>organisational challenges</u></p>	<p>1. A key challenge is the need for closer integration between Phase 3 clinical trials and the real world (Phase 4) so that the transition from pre-licence in a limited number of selected patients to “mass” use in a broad range of patients is better coordinated to ensure medicines with the right risk benefit/(cost) ratio are widely used in the appropriate groups of patients.</p> <p>2. A balancing of the relative merits of observational data and clinical trial data is also required that will lead to new techniques to marry the data in a way that will provide regulators, the NHS and importantly patients with information that will help ensure the risk benefit of each medication is matched with patients own risk profile.</p> <p>Issues of best practice with regard to governance of data are also in need of careful attention. Data protection, scientific and ethical approval systems, the Caldicott system, PIAG and other patient consent issues all need to be considered so as not to restrict scientific, public health research whilst protecting the rights and security of the public.</p> <p>Data is becoming ever more available and in growing volumes through new technologies. Analysis of such data requires skill sets that are in short supply. Additionally the task of managing such data in a way that makes it easily usable for research requires specific skills that are also in short supply.</p>	<p>Observational data= clinical data generated during the delivery of normal everyday care and as stored on currently available and widely used research databases such as GPRD (www.GPRD.com)</p>

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	<p><u>and underpinning training,</u></p>	<p>Investment in academic programs where working with large databases and management of real life (NHS) data is required to ensure the UK develops the epidemiological skills needed to take advantage of the riches in future systems.</p>	<p>Some of the largest database studies already take place in GPRD and require specialists' skills to manage the data, transform the data into a usable research format as well as correctly analyse the data. The GPRD group is therefore very aware of all these issues and of how the Secondary Users Services (SUS) of CfH, with the potential to offer 20 times more data than GPRD, may have serious problems unless these issues are properly addressed.</p>
<p>b) How might the UK Government best help address those challenges?</p>		<p>The UK system of healthcare delivery and the observational data already available within the UK (as exemplified by GPRD) are an ideal vehicle in which such integration can take place in conjunction with the other activities already planned under the UKCRC. Integration that will enable Pharma to recognise the additional benefits of undertaking greater volumes and more varied types of research in the England. There is a large pharmaceutical industry presence in the UK, although many of the database work takes place in the US.</p> <p>Connecting for Health presents an opportunity in the medium term to help such integration, however, the GPRD is already an accepted vehicle in which much work is already done but with additional central backing could achieve much more to create both improved health and wealth.</p> <p>In achieving more in the short term it would put CfH/SUS at a "running start" when it is able to deliver</p>	<p>The GPRD database owned by the Secretary of State for Health is:</p> <ol style="list-style-type: none"> 1. a 5.5%, 3 million active patients, representative sample (age, sex, geographic) of the UK population. It has been operating since the mid 1980's and consequently contains the longitudinal healthcare record that is so important to reaping the benefits of such data. 2. the full longitudinal record of all care (coded and text) stored within the gatekeeper GP computer system including all* primary care consultations, referrals, prescriptions, immunisations, laboratory tests, hospitalisations. <p>* All in this sense does not guarantee there is no missing data. However the database has been extensively validated and the level of missing data are at about the 1-5%. A level that gives GPRD a distinct advantage over other globally available datasets.</p> <ol style="list-style-type: none"> 3. the world's most used database when it comes to drug/vaccine safety, drug outcomes, drug utilisation research as well as economic research. There are over

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		<p>more or better than that that is currently available.</p> <p>The opportunity to marry the new technologies and ways of housing data being delivered by CfH with the expertise and global networks already being delivered by GPRD should be seized upon to deliver an important government objective for better research for better health.</p>	<p>research as well as economic research. There are over 500 peer reviewed publications on the database amassing nearly 2000 peer review impact points.</p> <p>The database has traditionally been used for observational research, however recent and on-going changes to the database mean that it is now in a position to offer a whole new range of services; services that can impact now on health and wealth. With the right impetus and it can be an important contributor to the work of the UKCRC and ensure earlier and wider success of many of their plans..</p> <p>4. already used either regularly or intermittently by most of the top 30 Pharma companies, many UK and overseas academics as well as drug regulators (MHRA, FDA). It is currently used as one of their major tools in ensuring drugs are safe and effective in everyday use as well more recently in meeting the requirements of Risk minimisation as required of new medications.</p>
<p>c) <i>What do you believe should be the Government's objectives for health research, and why?</i></p>		<p>To maximise the existing leverage that England and the UK has in the use of observational real world data, such as GPRD, now and use this as a platform for any added advantages that can be delivered by CfH.</p>	<p>The wealth of data housed within the NHS, if used to its potential should be made widely available i.e. within government, academia and the pharmaceutical industry. Utilising this resource new and better research can be conducted on, disease epidemiology, drug safety and effectiveness, resource planning and health economics, prescribing and treatment patterns.</p> <p>The global market for high quality, real life data is worth many millions of pounds per year although it needs to be managed ethically and responsibly. The investment potential in these data if new and existing data streams are married with experience and expertise such as that held in GPRD will return high dividends both in terms of finance but also in terms of public health.</p>

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	<p>Such an environment would further encourage the development of novel methods of ensuring that drugs have an acceptable risk benefit profile so ensuring that UK patients get the best benefit as well as showing global Pharma why it should invest more within the UK.</p>	<p>The GPRD research team is already working on three novel applications of data that will add to the health and wealth creation movement.</p> <p>Risk benefit profiles</p> <p>The GPRD research team has been working for some time on new techniques to better enable the results of phase 3 clinical studies to be amalgamated with real world observational data. This work will enable an improved understanding of the risk and benefit of medications at the person level; so enabling GPs with their patients to choose medicines that suit needs.</p> <p>Risk Tracking of new medication (dose and indication changes)</p> <p>Key to improving the safety of taking new medications is the ability of pharmaceutical companies and drug regulators to have earlier warnings on potential safety issues. GPRD has for sometime been working on a new system that Pharma companies can use under their Risk Management obligations to ensure that both potential risks, as identified in phase 3 clinical trials, can be monitored and potential new safety issues within the larger real world population can be identified.</p>
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			<p>Phase 4 randomisation into database studies-PROBED study</p> <p>Prospective Randomised Open label Blind.. End point Database</p> <p>Traditional clinical trials (Phase 2,3,4) are expensive to run because, in the main, they require special data collection methods and staff to ensure the study is conducted strictly to protocol. Phase 4 studies however should be run in a manner that is as close to the real world clinical situation as is possible- for that is what the study is about, how the drug performs in the real world.</p> <p>In a PROBED study, the only data that is collected additional to normal care is that the study participants are flagged as being randomised into a study. The intervention is Drug A (under test) versus B - any other care the doctor might have chosen for the patient. The only difference between normal care and care in a PROBED study is that the choice of A or B is by randomisation.</p> <p>Prescriptions are written in the normal way and care and events follow as in the real world. The data for the study is derived from the clinical care dataset- in our case GPRD. The study is event powered and would be terminated by the blinded end point committee when the accumulated events reach the level required for significance or at any earlier point should an untoward or</p>
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			<p>highly positive benefit be shown.</p> <p>PROBED studies: *can be run for both safety and benefit reasons *are highly cost efficient as the data collection is essentially automated and low cost. *can be run on large numbers by wide recruitment of GP practices *can help answer questions where channelling of new medications to essentially sicker patients is predicted to happen or where is it known or felt that residual confounding may give a misleading relative risk in a traditional database observational (non-randomised) study.</p> <p>England and the UK have natural advantages in the NHS, GP arrangements that with databases such as GPRD and the added potential for CfH could see the UK as being the place where Pharma would conduct these studies.</p>
3	<p><i>What should be the Governments priorities for health research?</i></p>	<ol style="list-style-type: none"> 1. Ensuring that any new and additional benefits from the outputs of CfH are maximised and delivered at the earliest opportunity by building on existing strengths already present within the system. 2. Ensuring that CfH/SUS learns from rather than compromises existing and well established research tools. 	

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	<p>3. To ensure that opportunities to combine the capabilities of existing “tools” are taken and maximised</p> <p>a). GPRD and Apollo software (data retrieval capabilities)</p> <p>This combination will provide the UK with a unique drug safety tool that has strong local health implications as well as far wider wealth implications</p> <p>b). GPRD and UK Biobank</p> <p>This combination we believe will improve the speed at which Biobank can get to research results as well as maximise the utility of extensive longitudinal patient data.</p> <p>c) GPRD and other UK datasets/registries</p> <p>The combination of up to 20 years longitudinal GP based healthcare history data with detailed data from disease registries offers exciting opportunities to better understand the factors that lead to disease as well as the way diseases progress.</p> <p>To formally encourage the concept of PROBED studies that can answer key questions about which medications/treatments for which type of patient in the fastest possible manner. It will also see the UK taking a further lead in providing the full portfolio of data required by Pharma to support the successful use of new medicines.</p>	<p>Apollo software is already used for QoF related work.</p> <p>Projects linking GPRD with cancer and Myocardial Infarction registries are in the planning stage but their development could be enhanced by setting such as a priority- a priority to maximise the existing assets of UK healthcare data.</p>
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<p>5.</p>	<p><i>a) In your experience, how have the results of publicly funded health research in the UK been used, both in the development of new treatments and to influence/change wider policy and healthcare practices?</i></p>	<p>Publicly funded research has until recently tended to focus on basic as well as developmental research and large scale phase 3 clinical studies. There has not been a history of funding observational research based upon real world data as found in NHS GP computer systems. However the recent MRC licence for GPRD data has been a positive move to enabling more UK academics to have access to such data.</p> <p>Publicly funded research carried out on GPRD has already influenced policy on a number of public health fronts. Including.</p> <p>SSRIs and suicidality</p> <p>This study undertaken by the MHRA provided important background information on the risks of suicidality in untreated depression and the use of antidepressants, as well as comparing the risk of suicidal behaviour in patients treated with different types of antidepressant drugs, including selective serotonin reuptake inhibitors (SSRIs). The results were used by the Committee on Safety of Medicines Expert Working Group on the safety of SSRIs to inform the development of suitable warnings which encompassed both the inherent risk of suicidal behaviour in untreated depression and appropriate prescribing advice (including information on risks) for this class of antidepressant drugs.</p> <p>Selective COX-2 inhibitors and cardiovascular risks</p> <p>In 2005 the Committee on Safety of Medicines issued revised prescribing advice for the selective Cox-2</p>	<p>The MRC licence with GPRD Group enables UK academics to have access to the GPRD and enables about 50 research studies per year for the next 5 years.</p>
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	<p>inhibitor anti-inflammatory drugs, used in the treatment of arthritis pain, following a European-wide review of the cardiovascular safety of these drugs. In order to evaluate the impact of the revised advice, the MHRA is currently undertaking a study using GPRD data to investigate the demographics of patients being prescribed these drugs. By comparing the characteristics of the patient population receiving COX-2 inhibitors prior to the new warnings with that receiving such drugs after the introduction of the revised advice, the MHRA will be able to establish whether or not the advice is being followed and consider whether additional action might need to be taken to ensure that COX-2 inhibitors are being used appropriately, to minimise the public health risk.</p> <p>Influenza vaccine and Bell's palsy</p> <p>Following a strong signal of an association between one particular form of influenza vaccine given intranasally and Bell's palsy (a neurological condition which results in facial paralysis), the GPRD was used to investigate whether such an association existed for the influenza vaccines used in the UK, which are given by injection (parenterally). The study, which was carried out by the MHRA in collaboration with the Health Protection Agency, found no evidence of a link between parenterally-administered influenza vaccines and Bell's palsy. The lack of association demonstrated by the research meant that the original signal could be discounted and the annual influenza vaccination campaign, involving over 5 million patients, could be continued with confidence.</p>	
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		<p>The new GMS Contract</p> <p>The GPRD was used for research funded by the Department of Health to develop a workload formula for use in the allocation of General Medical Services (GMS) resources at general practice level, adjusting for the age and sex structure of the practice population as well as its socio-economic and health status. The "Carr-Hill allocation formula" developed from this research has been implemented under the new UK GMS contract which was introduced in 2004.</p>	
	<p><i>b) What lessons can usefully be learned to improve the update of advances in science and medicine?</i></p>	<p>Clinical trials form an important part of the drug development and drug licensing regulatory process and when properly conducted are the gold standard. However such studies are run in limited populations with extensive exclusion criteria; often restricted to a single disease, a single treatment and in restricted age groups.</p> <p>The uptake of medicines is about use in the real world, post licensing, when drugs get used in a far more varied type of patient populations of all ages, taking a number of medications and having comorbidities. Additionally the numbers of patients taking drugs is of orders of magnitude greater than in the clinical trials so meaning that events rarer than about 1 in 3000 might not have been detected in the clinical studies. Detection of such events outside the clinical trial scenario is about using a combination of hypothesis generation methodologies (The Yellow card System) It is in this world that we need to understand the risk benefit profile.</p>	<p>Pharmacoepidemiology is the study of the use of and the effects of drugs, vaccines and devices in large numbers of people under normal everyday care. It encompasses drug safety (Pharmacovigilance), outcomes/drug effectiveness/utilisation research, pharmacoecconomics</p>

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	<p>Such research essentially comes under the umbrella of Pharmacoepidemiology; this is a relatively new branch of epidemiology that to a large degree relies on the availability of person level, but anonymised, longitudinal electronic healthcare records. Records that stem from a single database as available from NHS GP clinical systems (exemplified by GPRD) or that can be record linked together via an identifier such as the NHS number (exemplified by MEMO, in Scotland and by proposed linkage between GPRD and national cancer and cardiovascular datasets (MINAP) or that are proposed under SUS.</p> <p>However for success, pharmacoepidemiology research requires data that is as close as possible to the complete health record over time and importantly contains extensive historical data enabling proper establishment of prior disease or symptom history and volumes of data decided by the “power”¹⁷ required to produce a result that has significance and therefore can be acted upon. It might be imagined that large/very large datasets such as could be available via SUS are ideal as power is proportional to database size. However analysis of such large datasets will undoubtedly be a problem. The consequence therefore is that samples of data will remain being used</p>	
<p><i>b) How can UK health research be most effectively used to support the work of NICE, facilitate innovation and collaboration with industry, and address market failures in the application of healthcare?</i></p>	<p>This question specifically mentions NICE but perhaps could be asked as- to support the work of those agencies (MHRA, NICE, NPSA) involved with ensuring UK patients receive medications and treatments that have the most appropriate balance of effectiveness and safety i.e. the medications risk balance is appropriate for each individual, as judged</p>	

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	<p>by the patient in consultation with healthcare professionals. Equally important are the judgements about cost-effectiveness of medications that have major implications for the NHS budgets but equally major implications for patients and their care delivery.</p> <p>All this work is about the data and information available to make appropriate decisions at each key point in the life cycle of medications. From clinical trial data to observational real world data and modelling. At each stage in the life cycle there are merits of each of the three options.</p> <p>Observational data has already been used effectively to assess the impact of and compliance with NICE guidelines, and we know this is an area of research NICE are keen to utilise on a routine basis.</p> <p>Pre clinical studies</p> <p>Using Observational data to enable a full understanding of disease, patient profiles of those being treated, effectiveness of existing treatments, safety profile of existing treatments.</p> <p>Clinical studies Phase 2/3</p> <p>1. Using observational data to enable recruitment to clinical trials of suitable patients in large numbers. 2. Enabling researchers to estimate the power (number of patients/ events) required in order to run a suitable ethically acceptable study.</p> <p>Post Licensing-Phase 4</p> <p>1. Tracking of exposure to new medications and</p>	
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		<p>outcome to assess:</p> <ul style="list-style-type: none"> a) effectiveness b) safety profile in real world use- decreasing uncertainty (hypothesis strengthening) about issues raised in Phase 3 and obtaining information on side-effects that occur in less than n/3 where n is the number in the phase 2/3 clinical studies; typically 10,000 so meaning events occurring at only less than 1 in 3,333 (hypothesis generation). c) The profile of the patients exposed to the new medication so enabling a risk balance profile to be understood. This is now required under EU Regulations for all new products including dose changes and new indications. <ul style="list-style-type: none"> 2. Conduct observational case control, cohort or other such studies to test a hypothesis. 3. Conducting Phase 4 PROBED studies- Prospective, randomised, open label, blind end-point, database studies. 	
<p>9.</p>	<p><i>What lessons should the UK learn from other countries in making the proposed changes to the institutional arrangements for the funding of health research?</i></p>	<p>The USA has recognised the value of observational research/pharmacoepidemiology using real world data for the last few years. It has also recognised that although much PHARMAco-epidemiology will always be funded by PHARMA it is important that this is balanced with a significant level of government/healthcare related funding. The Agency for Healthcare Research (AHRQ) and in particular the AHRQ Centers for Education and Training on Therapeutics (CERTs) are providing federal support. The CERTS program is mandated by the authorisation for the FDA, brings together academic centres, government agencies, pharmaceutical companies and consumer advocates under core funding. The National Institute of Health has also begun to fund pharmacoepidemiology projects and there are on-going discussions with the National</p>	

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		<p>Institute of General Medical Sciences</p> <p>Developing countries whilst not providing any such funding have also begun to recognise there is an issue as they spend a disproportionate amount of their healthcare resources on drugs (ref) yet these drugs are often used inappropriately Ref)</p>	
<p>11. <i>To what extent does the success of recent innovations in health research (e.g. Clinical Research Networks) and the proposed structures rely on the new Connecting for Health NHS IT system, and to what extent should it do so?</i></p>	<p>Connecting for Health has the capability to improve the infrastructure that makes available data in an electronic and therefore easily researchable format. It also has implications for improving data quality. This in turn can improve how many aspects of research are and can be undertaken.</p> <p>However the same can also be achieved through record linkage of dataset by having the NHS number attached to all NHS person level data as was the proposal before CfH. In this record linkage model the right data can be obtained from the right system at the right time in order to gain the information/data required.</p> <p>CfH has the capability of delivering such record linkage at the 100% level and across all datasets that are deemed to be part of the CfH programme. However, such a system may not at the 50+ million level be able to offer a rapid service because of the sheer volumes of data, in both patient number terms and in the volume of record held on each individual.</p> <p>Additionally it is possible now, rather than waiting for CfH to deliver to make use of existing sample, generalisable datasets (such as GPRD) and of external record linkage to GPRD in which to conduct studies. Over the next 12 months record linkage of</p>		

Response from GPRD Group, MHRA

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		<p>GPRD to any dataset with the NHS number, Post code and or date of birth will become possible. There are already outline proposals for linkage studies to cancer registries and MINAP (Myocardial infarctions)</p> <p>Such projects taking place prior to the full capabilities of CfH should be seen as piloting the way forward so that CfH has a running rather than standing start.</p>	
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