ECONOMIC POST-LAUNCH STUDIES: MATCHING THE DESIRABLE WITH THE FEASIBLE

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CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1 – INTRODUCTION

1.1 What are post-launch economic studies?

Whilst companies routinely conduct post-marketing surveillance studies to collect data on adverse events, the focus of this report is on 'post-launch' studies conducted to collect information about health outcomes, including pharmacoeconomics data. By 'post-launch', we mean that they are undertaken after a drug has entered the market. This generally happens shortly after the product has received marketing authorisation in one country, which can be used as an 'index date' to establish post-launch status. Of course, drugs may receive a licence in one country whilst remaining 'pre-launch' in other settings. For the purposes of this report, we consider 'post-launch' studies to be those for products that have received marketing authorisation in at least one country.

Post-launch studies have attracted more interest since some jurisdictions have requested economic data as part of their formal decision-making process on the pricing, reimbursement or use of drugs. There has been a growing realisation that much of the data required by reimbursement agencies cannot easily be provided before the drug is marketed. For example, it is difficult to know whether the clinical effect observed in short-term clinical trials is maintained in the long run. Also, it is difficult to know how well patients will adhere to the new drug in regular clinical practice and the long-term consequences of their withdrawal from therapy. Prior to launch it may have been difficult to compare the drug, in head-to-head clinical trials, with the most relevant alternative products. This could be because, during phase III, drug-licensing agencies have mandated particular comparators, or the use of a placebo. Alternatively, it could be because the main competitor products were themselves, at that time, investigational drugs. Since post-launch studies are not generally mandated by licensing authorities, the principal reason for companies to undertake such research is to gather more data or evidence that will maximise the financial return from the product, either by maintaining price or increasing market access.

1.2 What are the costs, benefits and incentives in undertaking post-launch research?

Since economic studies post-launch are rarely mandated as part of registration or reimbursement procedures for pharmaceuticals, whether, what and how post-launch research is undertaken will therefore depends on several factors:

I. The costs of undertaking studies: what are they and who should pay?

II. The benefits (harms/risks) of studies: what are they and to whom do they accrue?

III. The incentives to undertake studies: what do various parties require, which incentives exist and what barriers may need to be overcome?

One method of evaluating the likely costs and benefits of post-launch research is the 'expected value of perfect information' (EVPI) approach, which has been explored formally by Claxton (Claxton, 1999, Claxton *et al.*, 2002). A key underlying premise of this approach is that decision uncertainty can be costly: a decision based on imperfect information may be wrong, and there will be consequences of making a wrong decision in terms of, say, unnecessary morbidity or mortality (Claxton, 1999). Additional information from post-launch research is valuable if it reduces the decision uncertainty. Investment in studies to obtain that information is justified only if the expected additional value of the information is greater than the expected additional cost of obtaining it, including associated reporting and treatment costs. The value of information approach offers an explicit decision-analytic framework that can make requests or recommendations for further research more efficient by helping to set priorities for research and providing guidance on the best study design (Claxton *et al.*, 2002).

Adopting a societal perspective for the value of information analysis will ensure that all relevant costs and benefits are considered. Whether post-launch research is cost-effective from the manufacturers'

perspective is a different question. Of course, some of the efficiency gains from additional information may be transferred to pharmaceutical manufacturers if, through the information being available, sales of their products increase. However, manufacturers also need to consider the risk and the financial costs of undertaking further research. Therefore, even if post-launch research is desirable and cost-effective for society, this is not necessarily the case for an individual manufacturer or for the pharmaceutical industry as a whole.

Regardless of the perspective adopted, *how* the research is undertaken – in terms of the choice of study design – also influences the cost-effectiveness of post-launch research. Broadly speaking, there is a trade-off between the cost of the study and the quality of information generated: well-controlled studies may generate good quality data but are likely to be more costly than observational studies. Furthermore, there is a methodological trade-off to be made between the precision of the study findings (their 'internal validity') and their generalisability (or 'external validity'). In this respect, the timing of costs and benefits is also important: if information is to be generalisable to the 'real world', then studies need to reflect clinical practice. As pre-launch studies are constrained by regulatory requirements, such studies are more likely to be undertaken post-launch. In addition, the relative burden of the cost of trials (i.e. between the manufacturer and payer) may vary depending on whether the manufacturer supplies the product free of charge (as is the case for pre-launch studies).

Governments or other payers for pharmaceuticals could insist that companies undertake various studies and hence bear the majority of the costs. Even then, the question of who pays in the long run will depend on the ability of manufacturers to pass on the costs of undertaking this research through higher prices. The potential for this will depend on prevailing market conditions. Nevertheless, the fact that the costs may be passed on illustrates that it is always in the decision-maker's interest to ensure that additional research would be socially efficient. The costs of additional studies can also be borne by different parties, or shared between those who stand to benefit.

The fact that the costs and benefits of post-launch research can be borne by different parties suggests that mechanisms may be required to bring private costs and benefits into line with societal ones. The most promising mechanism would be the use of incentives. This is why, on occasions, it may make sense to link the undertaking of post-launch studies with financial arrangements, such as risk-sharing or cost-sharing schemes. The worse case scenario would be to fail to recognise the potential deviation between societal and private costs and benefits, since this could lead to a situation where socially beneficial research is not undertaken because it is in no individual party's interests.

CHAPTER 2 – OVERVIEW OF METHODS

12 The report draws on a range of sources, including a comprehensive literature review, postal surveys of manufacturers and reimbursement agencies, and published recommendations for further research by the National Institute for Health and Clinical Excellence (NICE). Further details of the methods are provided in the Appendix.

The main focus of the report is on the UK. This reflects a number of factors including the prominent position of NICE, data availability and the accessibility of manufacturers. However, we also examine data from other EU countries where there is the potential for activity and consider the international implications of the findings.

CHAPTER 3 – WHY ARE POST-LAUNCH STUDIES RECOMMENDED OR CONDUCTED?

It is unusual for a post-launch study to be undertaken for a single reason. A given stakeholder may have several reasons for wanting the research to be conducted. Furthermore, even if the impetus behind post-launch research comes from a principal instigator – such as a payer or manufacturer – there may be other stakeholders with different interests in the same findings. We explored the motivations underpinning post-launch research from two principal perspectives: that of the payer and that of the manufacturer. Our findings are based on an analysis of published recommendations (NICE, England and Wales) and on postal surveys of European reimbursement agencies and of pharmaceutical companies (see Appendix section 10.1).

3.1 The Payers' Perspective

Our key question was 'what do reimbursement agencies (or the Health Technology Assessment (HTA) agencies that work for them) want to know about pharmaceuticals after launch?' We also wanted to know what type of study designs payers recommend. We explored the reasons why particular European reimbursement agencies recommend post-launch research, by analysing published recommendations (NICE, England and Wales) and by a postal survey of reimbursement agencies in the UK, France, Portugal, Sweden and Norway. Our reasons for selecting these countries were that they were either using economic analysis in reimbursement decisions, or were known to be active in promoting post-launch studies. In addition, a literature search was undertaken to provide background to the findings, to identity examples of post-launch studies and to uncover methodological and logistic issues debated in the literature.

3.1.1 Findings from the survey of European reimbursement agencies

We surveyed health technology agencies in five countries, asking them about the type of recommendations they make (for further details of the methods, see Appendix, section 10.1). An overview of these

agencies, informed by survey findings and by the literature review, is given in Table 1. France is given more detailed coverage than the other countries for two reasons. First, the recent and ongoing re-organisation of the French health care system means that there are relevant organisations that both pre-date the reforms and that have been created as part of the reforms (see Table 1). Secondly, France is presented in more detail to provide a contrast with the situation in England and Wales.

Compared with NICE, other European agencies make fewer and less frequent requests for post-launch data when making reimbursement decisions about medicines. The highest figure cited by an agency outside the UK was 40% (for the French Price Committee). The event is so unusual for the SLV (the Norwegian Medicines Agency) that our respondent was unable to cite an example. Reimbursement agencies in all countries consider clinical evidence and review economic dossiers submitted by manufacturers. Two agencies review additional economic data to inform reimbursement decisions: in England and Wales, NICE commissions external independent economic assessments and in Norway, the SLV conducts its own economic evaluations. All agencies recommended further studies to collect 'real world' data, particularly for informing patient pathways and assessing long-term effectiveness. Recommendations for studies to find specific items of data, such as quality of life, were rare.

3.1.1.1 Portugal

Established in 1993, the Portuguese National Institute for Pharmacy and Medicines (Instituto Nacional da Farmácia e do Medicamento; INFARMED) has statutory responsibility for medicine-related matters and for health products. The agency makes recommendations on the reimbursement and price of medicines and may negotiate with manufacturers on price or sales. The only economic evidence informing these recommendations comes from dossiers submitted by drug manufacturers, which is appraised and validated by INFARMED. The agency also carries out inspections of health care professionals and industry representatives, disseminates information to health professionals and monitors the pharmaceutical and health product markets. Recommendations for post-launch research are not routinely made as part of the agency's decisions on medicines, but occasionally head-to-head clinical comparisons, studies of the use of the drug in routine practice or the investigation of the drug in a different patient population are recommended. The agency never recommends studies to find specific items of economic data. The chief interest of the agency in 'real world' data is for long-term effectiveness, although its decisions indicate it is also interested in treatment sequencing, short-term effectiveness, adverse events, patient compliance and cost effectiveness. The preferred study design for collecting this type of data is randomised controlled trials (either explanatory or pragmatic), although the agency has occasionally recommended observational studies. Drug manufacturers were thought by our survey respondent to react positively to recommendations for RCTs, especially where pragmatic designs are specified. As well as a commitment by authorities and payers to revise their decisions on the basis of findings from post-launch studies, our respondent was of the view that sharing of costs by these parties had the potential to stimulate post-launch research.

Table 1 **Overview of the HTA/reimbursement organisations in five European countries**

Country	Body Acronym	Comments	Main functions/ reference	
England and Wales	National Institute for Health and Clinical Excellence NICE	Established in February 1999 as a Special Health Authority under section 11 of the 1977 Act (SI 1999/220): the National Institute for Clinical Excellence. Merged with the Health Development Agency to become the National Institute for Health and Clinical Excellence in April 2005	Four principal functions 1. Technology appraisals: guidance on the use of selected new and existing treatments within the NHS in England and Wales 2. Clinical guidelines: these offer guidance on the appropriate treatment and care of people with specific diseases and conditions within the NHS in England and Wales 3. Interventional procedures: guidance on whether interventional procedures used for diagnosis or treatment are safe enough and work well enough for routine use in England, Wales and Scotland 4. Public health	

[1] http://www.nice.org.uk/page.aspx?o=219813 (accessed 24/11/05)

	Type of information considered/ evaluated (source)	Role of government	Post-launch research
	Clinical effectiveness (literature/manufacturers) Safety (literature/manufacturers) Economic evidence: Technology appraisals (literature/ manufacturers/ independent assessments) Clinical guidelines (literature) Interventional procedures (none)	The Institute is an NHS body, accountable to the Secretary of State for Health and the National Assembly for Wales for its resources, delivery of its work programme and for the guidance it produces for the NHS[1] Appraisal products selected by the Advisory Committee for Topic Selection (ACTS) NICE technology appraisals are underpinned by statute. NHS funding bodies are under a statutory obligation to ensure that a recommended treatment "is, from a date not later than three months from the date of that Technology Appraisal Guidance, normally available" (Secretary of State for Health, 2001) Wales also operates the All Wales Medicines Strategy Group. Its advice, focussed only on high-cost drugs, is legally binding on Welsh health authorities. However, the Welsh Minister for Health may block the Group's advice	Most technology appraisals contain recommendations for further research. The recommendations cover a wide range of study designs and types of information that NICE perceives as being desirable to inform reimbursement decisions

Country	Body Acronym	Comments	Main functions/ reference	
Scotland	Scottish Medicines Consortium SMC	Established October 2001 (Anonymous, 2004) Consortium of all area drug and therapeutics committees of Scottish Health Boards	Advises Scottish NHS Health Boards on the status of all newly licensed medicines, new formulations and any major new indications for established products as soon as practical after the launch of a product. Process usually takes 8 weeks (Anonymous, 2004) SMC has formed a sub-working group named the New Drugs Committee (NDC) to advise and make recommendations to SMC 3 categories of recommendation: accepted for use, restricted use or not recommended for use	
France	Haute Autorité de Santé HAS	New organisation, created under the August 2004 Douste-Blazy reform (Rodwin and Le Pen, 2004), operational from January 2005	Takes over functions of ANAES, CdT, la Commission d'évaluation des produits et prestations (CEPP) and le Fonds de promotion de l'information médicale et médico-économique (Fopim) (Haute Autorité de Santé, 2005) Evaluates medicines and devices, relative to all relevant technologies and produces clinical guidelines Accreditation of health organisations; recommendations relating to chronic diseases; information technology reviews and certification; mandatory healthcare professional appraisal	

	Type of information considered/ evaluated (source)	Role of government	Post-launch research
	Clinical effectiveness (manufacturers/ literature) Cost-effectiveness (manufacturers) Safety (manufacturers) Manufacturers complete a New Product Submission form	Part of the Scottish Executive Health Department. Boards should ensure that '*unique*' drugs or treatments recommended by the SMC are normally made available to meet clinical need within 3 months of the publication of advice (Jones, 2003). For other drugs, implementation is decided by local Boards	About one-quarter of products reviewed are not recommended for use (Anonymous, 2004). Companies can resubmit with new evidence, although there is no formal feedback process to guide any resubmission The SMC may delay implementation, pending an audit of the drug (Jones, 2003)
	Evaluations and recommendations based chiefly on 'level of scientific proof', although relevant social science and economic studies also considered by certain subcommittees (Haute Autorité de Santé, 2005)	Described as a public and independent scientific organisation. The Ministry of Health may request information	See entries for Price Committee (CEPS) and Transparency Commission (CdT)

Country	Body Acronym	Comments	Main functions/ reference	
	Price Committee (Comité Economique des Produits de Santé) CEPS	Established in 2000[2]	Reimbursement/Pricing: CEPS considers general important (SMR), added value (ASMR), relative costs, budgetary impact, treatment sequence and ONDAM, the annual budget for which government may target certain therapeutic areas for cost savings (Furniss, 2001) Reimbursement at 35%, 65% or 100%; restrictions may apply	
	Transparency Commission (Commission de la Transparence) CdT	Established in 1967 (Décret du 67-441 du 5 juin 1967) and named the Transparency Commission in 1980 (Arrêté du 12 décembre 1980) Taken over by HAS in 2004	Review of approved drugs; findings may inform reimbursement and pricing decisions (Stafinski and Menon, 2003) Assessments of contribution of drug to health care: (a) general importance (SMR: Service Medicale Rendu) (b) advantage over existing therapies (ASMR: Amelioration du Service Medicale Rendu) (Anell, 2004) For reimbursement, drugs given SMR rating: 1. Of major therapeutic value 2. Of some therapeutic value 3. Of insufficient therapeutic value	

[2] http://www.sante.gouv.fr/ceps/sommaire.htm (accessed 24/11/05)

	Type of information considered/ evaluated (source)	Role of government	Post-launch research
	Economic evidence (i.e. cost: only for me-too products or generic alternatives)	Whilst the CdT advises government, final decisions are made by the CEPS under the auspices of the health minister, who also signs the final decree	Makes recommendations for approximately 40% of products reviewed, mainly studies on budget impact
	Clinical data from phase III trials: efficacy, adverse events Also considers treatment severity, treatment options, position in treatment pathway, benefit to public health (l'intérêt de santé publique, ISP) (Le Gales *et al.*, 2003) Long term outcomes data Subcommittee considers economic evidence	Advisory role to government	Reimbursement decisions re-evaluated after 3 years (Anell, 2004) Commissions post-launch studies for approximately 20% of products reviewed

Country	Body Acronym	Comments	Main functions/ reference	
			For pricing, CdT gives a comparative ASMR rating from 1 (major therapeutic advance) to 4 (minor improvement in efficacy or convenience) (Furniss, 2001) Reimbursement/Pricing: Determined by CEPS	
	l'Agence Nationale d'Accréditation et d'Evaluation en Santé ANAES	Established April 1996 (formerly ANDEM, set up in 1990)(Orvain *et al.*, 2004). Replaced by HAS in 2004	Evaluation of non-pharmaceutical health technologies (equipment, procedures, service delivery, screening) Hospital accreditation Codes/classification Draft clinical guidelines Horizon screening	
	Agence Française de Securité Sanitaire des Produits de Santé AFSSAPS	Established by law, July 1998 Formerly known as the French drug agency	Regulatory/monitoring activities for all health products (evaluation, laboratory controls, on-site inspections) (Orvain *et al.*, 2004) Market authorisation of pharmaceuticals Monitoring of pharmaceuticals and devices, to determine whether to restrict use, redefine indications or conditions of patient follow up	
	Fonds de promotion de l'information médicale et médico-économique Fopim	Established in March 2002[3] Replaced by the "quality of medical information commission" of the HAS	To provide professionals with clear, scientifically valid public health information, to inform the appropriate use of medicines in clinical practice[3]	

[3] http://www2.fulmedico.org/a/article.php?id_article=182 (accessed 24/11/05)

	Type of information considered/ evaluated (source)	Role of government	Post-launch research
	Systematic literature review to assess clinical, economic and safety issues Expert opinion panel Survey of practice	In 2002, 55% of requests for HTA reports came from the Ministry of Health (DGS) or Department of Social Security ANAES advises decision makers	Advise on further research, clinical or economic
	Scientific, medical and economic evaluation of pharmaceuticals (note economics data not used to inform marketing approval)	Government body Safeguards public interest, health promotion Exerts control over relationships between organisations that finance health care, health professionals and patients and defines the rules of health care coverage (Orvain *et al.*, 2004)	NA
	Database of pharma-ceutical information to be accessed by doctors via prescribing software	No official role	NA

Country	Body Acronym	Comments	Main functions/ reference	
Norway	Norwegian Medicines Agency (Statens legemiddelverk) SLV[4]	Established in 2001	Regulator of new and existing medicines Supervision of production, trials and marketing of medicines Grants marketing authorisation for new medicines Makes reimbursement decisions Monitors medicine use Regulates prices and trade conditions	
Portugal	National Institute for Pharmacy and Medicines (Instituto Nacional da Farmácia e do Medicamento) INFARMED	Established in 1993 The INFARMED is the statutory body responsible for matters dealing with medicines for human and veterinary use and health products (devices and non-medicinal products) ((Stafinski and Menon, 2003)	Evaluation issues related to the marketing of medicines (reimbursement/ pricing) Quality assurance Monitoring of adverse drug reactions Economic evaluation (appraisal of manufacturers' economic studies) Subsidised pricing of medicines Trial regulation[5] Licensing of manufacturers, wholesalers and pharmacies[5] Dissemination of scientific findings to healthcare professionals and to the public[6]	

[4] http://www.legemiddelverket.no/templates/InterPage____15421.aspx (accessed 24/11/05)
[5] http://www.infarmed.pt/en/instituicao/about.html (accessed 24/11/05)
[6] http://www.infarmed.pt/en/instituicao/areas.html (accessed 24/11/05)

	Type of information considered/ evaluated (source)	Role of government	Post-launch research
	Pharmacoeconomic analyses, submitted to inform reimbursement decisions Evidence of clinical benefit (if not covered in pharmacoeconomic submission)	SLV has to reject reimbursement applications if net additional annual drug costs are estimated to exceed 5 million NOK (around £0.4m). However, SLV assesses the cost effectiveness of the new drug compared to alternative treatments for the same condition. If considered positive by SLV, the Norwegian government or Parliament makes priority decisions in the yearly budget process regarding investment in the new drug compared to other proposed initiatives, both in health care and other sectors	SLV may suggest that post-launch research is undertaken, although this is rare
	Clinical effectiveness (literature/manufacturer) Safety (literature/ manufacturers/ pharmacovigilance) Economic evidence (manufacturers)	INFARMED is a government agency accountable to the Health Ministry. INFARMED does not set prices, but may engage in negotiations with manufacturers about price	Recommendations for post-launch studies are unusual (2% of products reviewed). When these occur, they focus on new clinical head-to-head comparisons and 'real world' data collection

Country	Body Acronym	Comments	Main functions/ reference	
Sweden	Swedish Council on Technology Assessment in Health Care (Statens beredning för medicinsk utvärdering) SBU	Established in 1987 (Carlsson, 2004)	To continuously update the government and health care providers with scientific information about the overall value of medical technologies Three to four full assessments of particular topics annually SBU Alert: brief assessments of new and emerging technologies	
	Pharmaceutical Benefits Board (Läkemedelsförmåns nämnden) LFN	Established in October 2002 Other local HTA agencies	Pricing: LFN considers price as part of the cost effectiveness evidence (Stafinski and Menon, 2003) Subsidy: LFN decides whether drug is subsidised 4 principles in Act of 2002: 1. Human dignity (equal opportunity) 2. Resources reflect need 3. Cost-effectiveness 4. Marginal utility Supported by Swedish Parliament's 'guidelines on prioritisation' (cost/QALY) (Anonymous, 2003)	

	Type of information considered/ evaluated (source)	Role of government	Post-launch research
	Effectiveness/cost-effectiveness (systematic literature review) SBU Alerts: Risks, ethical concerns, organisational impact	Parliament and the Department of Health and Social Affairs suggest broad health issues for SBU to prioritise (Carlsson, 2004) Department of Health and Social Affairs produces national guidelines, based on SBU reports. Some county councils have formal links with the SBU (Carlsson, 2004)	
	Health impact (clinical effectiveness; disease severity) Quality of life Cost Note: economic evidence is requested for orphan drugs, although this is not always available (manufacturers' submissions)	Legislation created LFN and directs decision-making Local government enjoys a high degree of autonomy. The 21 county councils are responsible for meeting the healthcare needs of their population and for provision of public finance for healthcare. Municipalities are responsible for long-term care of the elderly and for social services (Carlsson, 2004)	Approximately 20% of agency decisions on medicines include recommendations for post-launch research Where approval is conditional, manufacturers must undertake prescribing audits and long-term follow up studies Marketing literature must reference approved indications LFN assesses both new and older drugs (Carlsson, 2004)

3.1.1.2 Sweden

Sweden's Pharmaceutical Benefits Board (Läkemedelsformånsnämnden; LFN) was established in 2002. Like the Portuguese agency, the Swedish agency neither undertakes pharmacoeconomic analyses nor commissions economic evaluations from external bodies, but relies on the analysis and interpretation of economic data submitted by manufacturers. About 20% of the LFN's decisions on medicines contain a recommendation for further research and these typically relate to the use of the drug in routine practice and/or in different patient populations. Head-to-head clinical comparisons are not requested. There is a high level of interest in treatment sequencing, long-term effectiveness, patient compliance and cost effectiveness. Considerations of adverse events and safety issues are outside the remit of the LFN. The LFN recommendations never stipulate that RCTs should be conducted, but do sometimes advocate free-standing, empirical studies. Where an approval for reimbursement is conditional, manufacturers may be required to undertake administrative database analyses or clinical case series studies (e.g. prescribing audits). Our survey respondent indicated that manufacturers always act upon the LFN's recommendations and was of the view that less emphasis on randomised designs could encourage more post-launch research.

3.1.1.3 Norway

The Norwegian Medicines Agency (Statens legemiddelverk; SLV) was established in 2001. The SLV regulates new and existing medicines and may occasionally recommend post-launch research. In making decisions about medicines, the agency undertakes its own economic evaluations as well as reviewing manufacturers' economic dossiers and will review further clinical evidence if necessary. In terms of encouraging more post-launch research, the only factor considered by our survey respondent to be influential was the commitment by authorities / payers to revise decisions on the basis of findings from these studies.

3.1.1.4 France

In France, there are multiple agencies that make decisions about medicines (Table 1). In August 2004, France enacted the Douste-Blazy reform (Rodwin and Le Pen, 2004). January 2005 saw the implementation of these reforms, which are designed to address the severe financial crisis facing the national health insurance system through "vast institutional renovation" (Rodwin and Le Pen, 2004).

There are two committees that make decisions about post-launch studies. The Commission de Transparence (CdT) (The Transparency Commission), which was originally part of the AFSSAPS (Orvain *et al.*, 2004), is now part of the new Haute Autorité de Santé (HAS). The Transparency Commission makes decisions on new medicines, issues guidance on their appropriate use and has a subgroup whose remit is to review economic dossiers submitted by manufacturers. The second committee that makes recommendations about post-launch research is the Price Committee (Comité Economique des Produits de Santé, CEPS), which manages the budget for all reimbursed drugs and ensures the 'macro economic' regulation of the industry. Regarding recommendations for post-launch research, the proportion of decisions on new medicines affected is around 20% for the Transparency Commission and about 40% for the Price Committee. Both organisations are interested in the 'real world' performance of drugs, especially about treatment pathways. The Transparency Commission is very interested in short- and long-term effectiveness and moderately interested in adverse events and patient compliance. The Price Committee may ask for budget impact studies. The Transparency Commission sometimes recommends randomised designs, analyses of administrative databases and, rarely, case series studies for post-launch research. If the Price Committee advises reviews of administrative databases, then the methodology has to be validated by the Transparency Commission. Manufacturers sometimes respond to requests for post-launch research. However, the Framework agreement 2003-2006[7] between the government and the pharmaceutical industry stressed the importance of 'real world' data for new medicines (Article 6). In particular, the Transparency

[7] http://www.leem.org/industrie/legal13.htm. (accessed 24/11/05)

Commission might request studies for (i) medicines used by a wide patient population; (ii) medicines expected to be used in unlicensed indications, where safety and effectiveness are indeterminate; and (iii) medicines likely to have a significant impact on the organisation of the health system. In general, these studies will draw on data from health insurance organisations, be conducted in accordance with national guidelines and there is a duty to publish the findings.[7] Both the Price Committee and the Transparency Commission review the findings, which will inform the medicine's registration renewal. Study costs need to be reasonable ("*raisonnable*") i.e. proportionate to the sales value of and tax payable on the drug. Should the cost be disproportionate or if, for public health reasons, the study has to extend to include a wider, or different, patient group, the extra costs incurred will be compensated for by reductions in contractual fees.[7] Factors thought by our survey respondent to encourage post-launch research included cost-sharing by the authorities and payers and a commitment by authorities and payers to revise their decisions based on post-launch study results.

3.1.2 Findings from the analysis of NICE recommendations for further research

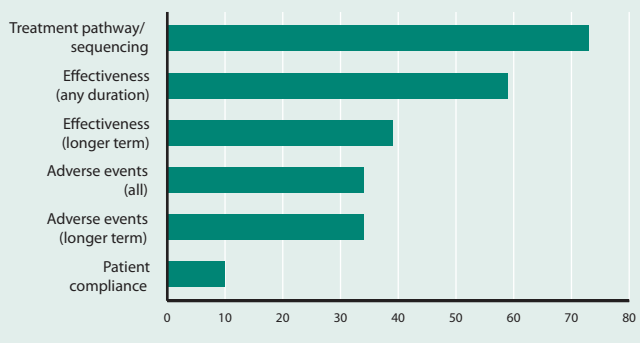
The National Institute for Health and Clinical Excellence was established in 1999. The Institute does not make recommendations about the price of medicines, but does issue guidance on the use of new and existing health technologies, including pharmaceuticals, in England and Wales. The NICE Appraisal Committee is an independent advisory body constituted of individuals drawn from a range of professional backgrounds (National Institute for Clinical Excellence, 2004). Clinical experts and user representatives may give evidence on the nature of the health condition and the benefits of the technology, and members of the assessment team are present to clarify the assessment report findings on clinical and cost effectiveness research (Table 1). The Committee bases its decisions primarily on the assessment report and on evidence from stakeholders, such as manufacturers. Part of this evidence includes economic evidence, which is

provided by manufacturers, external bodies and NICE's own analyses. All guidance is reviewed at regular intervals and recommendations reconsidered in the light of any new evidence. It should be noted that the overwhelming majority of technologies used in the NHS are not appraised by NICE.

When NICE publishes an appraisal, the guidance almost always includes recommendations for further research. We undertook an analysis of pharmaceutical appraisals that were published before January 2004. From a total of 73 appraisals, 48 addressed pharmaceuticals and 47 of these contained at least one recommendation for some type of post-launch research. Our analysis of these 47 technology appraisals found that NICE research recommendations fell into four broad categories. First, 42 of the 47 appraisals, having identified gaps in the evidence base, asked for studies to find *specific items of data*. Of these 42 appraisals, recommendations were made for further evidence on cost effectiveness (30 appraisals), data on quality of life (25) and data on disease progression or epidemiology (11).

Second, most appraisals (41/47) contained recommendations for further research to find *real-world data*, such as patient compliance or treatment sequencing. Figure 1 depicts the key types of 'real-world' data that NICE considered to be missing from the evidence base.

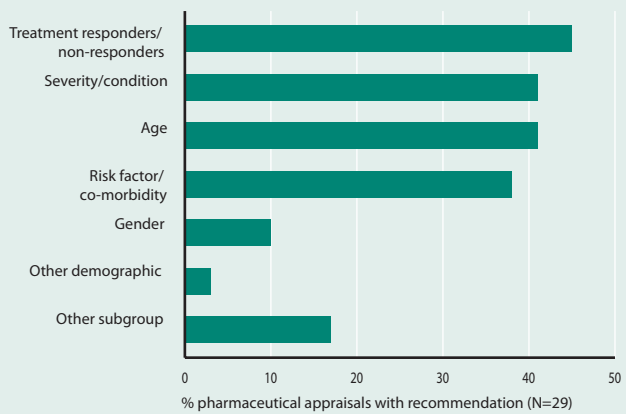
Figure 1: **NICE recommendations for 'real world' data: 1999 to 2003**



From these 41 appraisals, the sources most often specified for obtaining these data were audits and database registries (13 appraisals). Information about treatment pathways and drug sequencing (30), longer-term effectiveness (16) and adverse events (14) were highlighted as topics for further research. Just four appraisals specified the need for more evidence on compliance with therapy in usual clinical practice.

The third broad category of evidence contained in NICE research recommendations concerned the impact of the drug in *particular patient populations*, which was found in 29 of the 47 pharmaceutical appraisals. This relates to NICE's interest in identifying those patient groups for whom a drug is particularly beneficial and hence cost-effective. Figure 2 shows the subgroup analyses recommended by NICE.

Figure 2: **NICE recommendations for subgroup analysis: 1999 to 2003**



Subgroups identified in research recommendations included patients with particular clinical conditions (12 appraisals) or co-morbidities (11), and patients of a particular age (12) or gender (3). Research was also recommended on the longer-term effects of the drug in patients who had responded, or had failed to respond, to treatment during a short-term clinical trial (13), since these factors could affect the long-term cost effectiveness of a new medicine. Most appraisals (18/29) recommended multiple subgroup analyses. For example, Appraisal No. 14 (Guidance on the use of ribavirin and interferon alpha for hepatitis C) advised research into patients with mild-to-moderate disease; trials of intravenous drug users; and trials of patients who had failed to respond to interferon alpha monotherapy.

Fourth, *head-to-head comparisons of one drug against another* were recommended in 21 of the 47 appraisals. The main areas of interest in these appraisals are shown in Table 2.

Table 2: **Types of study design recommended in NICE Appraisals, 1999-2003**

Types of Post Launch study	**No. of NICE Appraisals*** **	**% NICE Appraisals (N=47)*** **
New head-to-head clinical trials (all)*	21 [11]	45% [23]
New head-to-head clinical trials (combination)**	11 [6]	23% [13]
New head-to-head clinical trials (pragmatic)	11 [3]	26% [6]
New head-to-head clinical trials (efficacy)	15 [10]	30% [21]
Randomised controlled trials (all)	13 [13]	28%
Audits	13	28%
"Registry"	4	9%
"Case series"	1	2%
"Cohort"	1	2%
"Observational"	1	2%
No study design specified for any recommendation	13	28%

* Some appraisals recommended more than one type of head-to-head trial
** These are trials evaluating polytherapy
*** Number and percentage of requests specifying randomised trials given in parentheses

Thirteen appraisals (28%) specified the need for a randomised controlled trial (RCT), of which 11 were for new head-to-head comparisons (Table 2). Two appraisals recommended RCTs that were not new head-to-head comparisons. Firstly, NICE Appraisal No. 61 (Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer) recommended further trials comparing the same drugs as in previous RCTs, but with the comparator administered by infusional regimens, rather than by bolus injection. Secondly, NICE Appraisal No. 35 (Guidance on the use of etanercept for the treatment of juvenile idiopathic arthritis) recommended that further RCTs should measure economic outcomes. Two of the 13 appraisals that made no specific recommendation about study type referred to the existence of ongoing studies and a further six simply indicated that further studies should be of good quality without specifying study design.

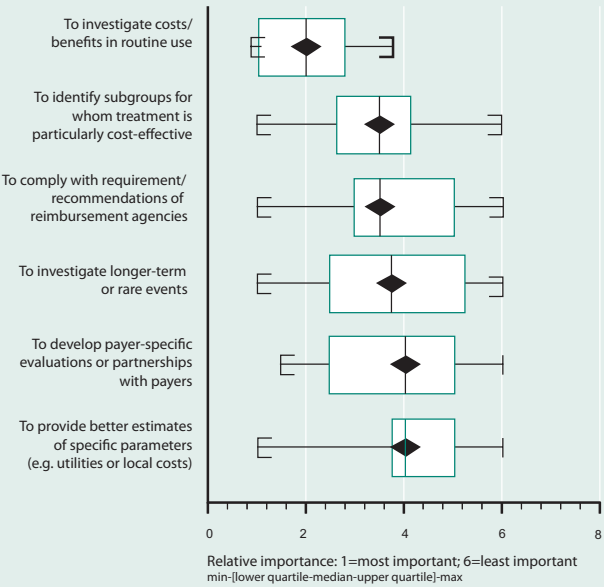
NICE recommendations rarely specified which party should be responsible for funding post-launch research, with most recommendations phrased in the passive tense ("Research is needed to…"; "Studies are required to…"). The exception to this rule was for Appraisal No. 32 (Multiple Sclerosis), which encouraged Trusts and health authorities to collect data (National Institute for Clinical Excellence, 2002).

3.2 The Manufactures' Perspective

We asked both Global and UK Heads of pharmacoeconomics / outcomes research about their motivations for undertaking post-launch research. As the question was identical in the two questionnaires, responses were pooled (see Appendix, section 10.1.4).

Respondents to both surveys ranked the investigation of costs and benefits in routine use in their top two, which was reflected in the pooled findings (Figure 3). Few other clear patterns emerged from the surveys, with no clear consensus apparent irrespective of whether findings from the two surveys were considered separately or together. Respondents were given the option of specifying their own priorities

Figure 3: **Rankings of motivations for undertaking post-launch research: pooled findings from the surveys of Global and UK Heads, 2004 (N=25)**



for undertaking post-launch research. Two Global Head respondents offered alternative 'top priorities', namely to support additional evidence-based messages for a product and to support marketing activities for specific markets or market segments. Only two of the fourteen companies who responded to our survey of UK Heads said that they had undertaken post-launch research on a named product as a direct response to NICE recommendations. One of the companies had undertaken an observational study to find out more about current treatment and prescribing patterns and the other had conducted post-marketing surveillance, a free-standing study and a prospective observational study.

CHAPTER 4 – WHAT SORTS OF STUDIES ARE CARRIED OUT?

There are many different types of study design that post-launch research may adopt (Table 3). Experimental studies are those in which the allocation to intervention or control is determined by the investigator, or random. In observational studies, patients receive usual care and no attempt is made to influence clinical practice.

Table 3: **Types of study design used in post-launch research for pharmaceuticals**

Study Design	Description	Purpose
RCTs (explanatory)	An experimental study in which carefully selected participants are randomised to receive an intervention or control treatment. Comparison groups may receive placebo or active drug. Participants follow a strict care protocol that may not reflect usual care.(explanatory)	Compares product with two or more competitor products not compared in Phase III. The intention is to assess drug efficiacy under optimal conditions.
RCTs (pragmatic)	Similar to explanatory RCT, but with less restrictive eligibility thresholds and care protocols. Includes PROBE (Prospective Randomised Open-label Blinded Endpoint) studies	Compares product with a relevant alternative in a practical setting: economic data may also be collected. The intention is to assess drug effectiveness under 'real world' conditions.
Non randomised comparisions	In quasi-experimental studies, the investigator determines allocation to comparison and intervention (i.e. allocation is non-random); controls may be matched and the analysis adjusted for any remaining (known) between-group differences. Non-randomised comparisons include controlled observational studies such as case-control studies and cohort studies, both of which may be retrospective or prospective.Cohort studies, which concurrently evaluate two groups, are considered more reliable than studies that make comparisons with historical controls.	Compares product with other competitor products, typically those representing usual care.

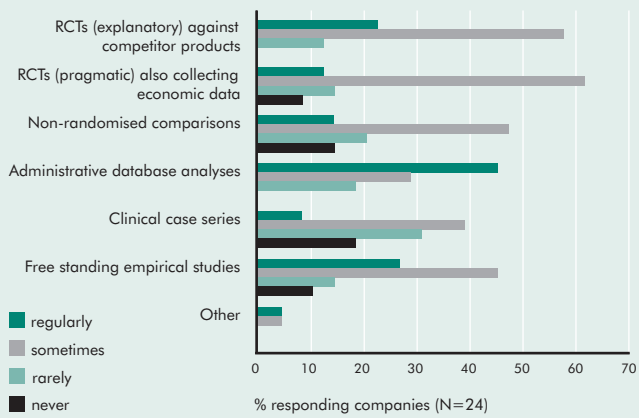
Sources: (Clarke and Oxman, 2003, NHS Centre for Reviews and Dissemination, 2003, Berger *et al*., 2003)

To study compliance or use of a drug in routine practice, an analysis of administrative databases or a clinical case series study may be undertaken. A 'free standing' empirical study, that is separate from trials undertaken to support licensing applications, can be used to assess particular variables such as quality of life or resource use. The appropriate choice of study design for post-launch research will depend on several factors, such as design strengths and weaknesses, the nature of the research question, the available resources and ethical considerations.

4.1.1 Findings from the surveys of Heads of outcomes research

In our surveys of both Global and UK Heads of outcomes research, we asked about the type of post-launch research currently undertaken by pharmaceutical companies (Figure 4; see Appendix, section 10.1.4 for details of pooling methods). Most companies we surveyed regularly, or sometimes, undertake RCTs post-launch, whether of explanatory (81%) or pragmatic (75%) design. In addition, analyses of databases (75%) and free standing empirical studies (73%) were frequently conducted post-launch.

Figure 4: **Types of post-launch study undertaken by pharmaceutical companies: pooled findings from the surveys of Global and UK Heads, 2004**



4.1.2 Case studies of post-launch research

A number of examples of post-launch studies were identified from our literature review and surveys. Table 4 provides a brief overview of the studies we selected to reflect the different motivations for undertaking post-launch research. We confirmed that studies included a post-launch period by checking the start date for the study against the approval date for the drug(s) in the country in which the study was carried out. However, sometimes the paper did not report the study start date, and so it was not always possible to confirm the true status of the study.

The post-launch studies described here cover some important topics facing society. For example, the question of whether hormone replacement therapy should be given routinely to post-menopausal women was addressed by the HERS trial (one paper reporting a particular aspect of the findings is given in Table 5) (Kanaya et al., 2003). Without a careful exploration of the benefits and risks of this therapeutic option, many women could be denied potentially health-enhancing treatment or, conversely, needlessly incur risks to their health. Equally, the treatment of depression in elderly people is a problem commonly faced in general practice and other outpatient settings; evidence to inform doctors about the appropriate role of pharmacological therapies in this patient group could therefore be very valuable to both patients and their doctors and carers.

Only one of the studies assessed costs and resource use data. Based on this small sample of studies, it appears that in post-launch research, as with pre-launch research, the emphasis is on collecting clinical data. Findings from our surveys of Global and UK Heads of outcomes research lend some support to this observation, with both sets of respondents reporting that explanatory RCTs were undertaken more frequently than studies that are more likely to include resource use data such as pragmatic RCTs or free standing empirical studies (see section 4.1.1). However, a systematic review of post-launch research would be needed to verify this.

Table 4: **Post-launch studies: rationale**

Author	Study design	New clinical head-to-head trial	Use of drug in real world
Ascher-Svanum, 2004	Prospective, controlled observational study		✓
Condemi, 1997	RCT, double-blind, placebo-controlled /active controlled	✓	
Genovese, 2002	Double blind, active controlled RCT		
Kanaya, 2003	RCT, double-blind, placebo-controlled		✓
Prasher, 2002	RCT, double-blind, placebo-controlled		
Prasher, 2003	Open label extension study		
Schneider, 2003	RCT, double-blind, placebo-controlled		

* Sources
FDA Website http://www.fda.gov/cder/index.html (accessed 21/04/05)
IMS British Pharmaceutical Index (BPI)

es and evidence of post-launch status

Investigation of drug in new patient populations	Studies to find specific items of data	Study start date	Approval dates (in trial setting)*
	✓	July-97	Olanzapine (FDA: Sept-96); risperidone (FDA: Aug-94)
		NS	Fluticasone (Flovent) (FDA: Mar-96); Triamcinolone (Azmacort) (FDA: Oct-96)
	✓	May-97	Etanercept (FDA (for RA): Feb-98); MTX: 1988
		Jan-93	Prempro / Premphase (FDA: Dec-94)
✓		NS	Donepezil licensed in UK February 1997 and launched in April 1997
✓	✓	NS	Donepezil licensed in UK February 1997 and launched in April 1997
✓		Jul-97	Sertraline (FDA: Nov-00)

Table 5 **Post-launch studies: summary of key characteristics**

Author	**Study design** **Study duration** **N enrolled**	**Setting** **Blinding**	***Classification*[8]** **Principal rationale[9]**	**Interventions**	
(Ascher-Svanum *et al.*, 2004)	Prospective, controlled observational study 1 year 271	US 6-centre study covering a range of care settings Open	*Use of drug in real world* To compare the risk of hospitalisation of treatment-adherent patients in the usual care setting for two antipsychotic drugs	Olanzapine (mean daily dose: 14.5 mg) Risperidone (mean daily dose: 4.5 mg)	
(Condemi *et al.*, 1997)	RCT, double-blind, placebo-controlled/active controlled 24 weeks 291	US 24 outpatient centres Double blind	*New clinical head-to-head trial* To establish efficacy and safety differences between inhaled corticosteroids	Fluticasone propionate and (triamcinolone acetonide dummy inhaler with) placebo Triamcinolone acetonide and (fluticasone propionate dummy inhaler with) placebo Placebo (triamcinolone acetonide	

[8] See section 3.1.2
[9] as stated by study authors

	Inclusion criteria **Exclusion criteria**	**Outcome measures** **Costs included**	**Study Characteristics**	**Main findings**	**Comments**
	Adults (>=18) with schizophrenia, participating in 3 year observational study, who continued on index antipsychotic at least one year after initiation Recent participation in controlled clinical trial, unable to give informed consent	Outcome measures used to proxy 'relapse': hospitalisation rate; inpatient days per patient; time to first hospitalisation Yes	Included many types of patient normally excluded from clinical trials (pregnancy, lactation, co-morbidity, substance abuse were not exclusion criteria). No formulary restrictions on patients, no treatment pathway specified. Patients with DSM-IV criteria for schizophrenia, schizoaffective disorder and schizophreniform disorder included	Treatment-adherent schizophrenia patients who were treated in usual care with olanzapine had a lower risk of psychiatric hospitalization than risperidone-treated patients. Lower hospitalization costs appeared to more than offset the higher medication acquisition cost of olanzapine	Part of a large study, the US Schizophrenia Care and Assessment Program (US SCAP; N=2327). Statistical analyses undertaken to adjust for potential confounding factors and for skewed hospital outcome data. Findings supported by previous research (2 RCTs) although retrospective studies provide a 'mixed picture'
	Non-smokers aged at least 12 who required maintenance inhaled corticosteroid therapy for at least 4 wks before the study commenced. FEV between 50 and 80% of predicted normal values and having at least one emergency or urgent episode in previous 12 months	Morning, predose forced expiratory volume (FEV); probability of remaining in study (not withdrawn through lack of efficacy); peak expiratory flow (PEV); albuterol use; night time awakenings requiring albuterol use; asthma symptom	Used standard dosing regimens	Fluticasone propionate powder twice daily (500 mcg/day) was superior in efficacy to triamcinolone acetonide aerosol four times daily (800 mcg/day) in patients with persistent asthma	Similar trial measured quality of life in 304 patients (Gross *et al.*, 1988)

Author	**Study design** **Study duration** **N enrolled**	**Setting** **Blinding**	***Classification*[8]** **Principal rationale[9]**	**Interventions**	
				dummy inhaler) and (fluticasone propionate dummy inhaler) placebo	
(Genovese *et al.*, 2002)	Extension study following double blind, active controlled RCT 1 year 512	US 11-centre study Single blind (radiographic assessor only)	*Study to find specific items of data* To find longer term efficacy and safety data	Etanercept (10 mg or 25 mg 2x/wk, by subcutaneous injection) and placebo pills Methotrexate (MTX) (mean weekly dose: 19 mg) and placebo injections. All patients received adjunctive folate.	
(Kanaya *et al.*, 2003)	RCT, double-blind, placebo-controlled 4-5 years 2763	US 20 clinical centres Double blind	*Use of drug in real world* To assess whether hormones have an impact on incidence of diabetes	Conjugated estrogen (0.625 mg) plus medoxyprogesterone acetate (2.5 mg) OD Placebo OD	

Inclusion criteria Exclusion criteria	Outcome measures Costs included	Study Characteristics	Main findings	Comments
Pregnancy, lactation, some concomitant medicines, significant concomitant illness	scores; adverse events; plasma cortisol concentrations No			
Adults (>=18) with rheumatoid arthritis (diagnosis <=3 yrs) and with no previous MTX treatment history. At high risk of radiographic progression. Treatment completers from double blind trial (Bathon *et al.*, 2000) Significant concomitant illness	ACR (American College of Rheumatology) scores (endpoint and change); Sharp scores (radiographic assessments of erosion and joint space narrowing); Health Assessment Questionnaire (HAQ) Data on quality of life (disability index) also assessed, but utilities not reported No	One-year extension of double-blind 12 month RCT (N=632), the Enbrel ERA (early rheumatoid arthritis) trial (Bathon *et al.*, 2000) No crossover	Etanercept as monotherapy was safe and was superior to MTX in reducing disease activity, arresting structural damage, and decreasing disability over 2 years in patients with early, aggressive RA	Improvements in arthritis (ACR scores) in the Enbrel 25 mg group were not significantly different to the MTX groups
Menopausal women aged <80 years with established CHD Women reporting CHD event within 6 months after randomisation excluded from analysis. Also those with high serum	Blood glucose level, incident cases of diabetes No	The principle outcome of the HERS trial was prevention of coronary events in women with established CHD. Kanaya and colleagues report the effect on the incidence of diabetes	Post menopausal therapy reduces the incidence of diabetes in women with coronary heart disease by 35%, but this is insufficient to recommend the use of hormones for secondary	A 2.7 year follow up of the HERS trial (HERS II) identified predictors of heart failure, of which diabetes was the strongest risk factor (Bibbins-Domingo *et al.*, 2004)

Author	**Study design** **Study duration** **N enrolled**	**Setting** **Blinding**	***Classification*[8]** **Principal rationale[9]**	**Interventions**	
(Prasher *et al.*, 2002)	RCT, double-blind, placebo-controlled 24 wks 30	UK Single outpatient centre Double blind (patient/assessor; investigator not blinded)	*Investigation of drug in new patient populations* Alzheimer's disease is common in middle-aged and older adults with Down's Syndrome, but only case studies of the use of anti-dementia drugs in this patient group are available	Donepezil, 5 to 10 mg, OD Placebo OD	
(Prasher *et al.*, 2003)	Open label extension study 80 weeks 25	UK Single outpatient centre Open	*Investigation of drug in new patient populations* To establish the long term efficacy and safety of anti-dementia drugs in people with Down's Syndrome (DS)	AOD (Always on donepezil – in trial and open study period) NOD (never on donepezil) Donepezil in trial, not open label period Donepezil in open label period, not trial	

Inclusion criteria Exclusion criteria	Outcome measures Costs included	Study Characteristics	Main findings	Comments
triglyceride levels, fasting blood glucose levels or uncontrolled hypertension		Although not a secondary end-point, the trial had assessed blood glucose level	prevention of heart disease	HERS also identified an increased risk of venous thromboembolism associated with this type of hormone therapy in this patient group (Grady *et al*., 2000)
Patients with Down's Syndrome and mild to moderate Alzheimer's disease living with carer Patient not ambulatory; significant co-morbidity or sensory impairment	Dementia Scale for Mentally Retarded Persons (DMR), Severe Impairment Battery (SIB), Neuropsychiatric Inventory (NPI), Adaptive Behaviour Scale (ABS). Side effects (modified COSTART dictionary). Carer questionnaire No	Allocation by sealed envelope, but these were allocated by alternation. This means that concealment of treatment allocation was inadequate and that findings may be affected by selection bias.[17]	Treatment may be effective for mild to moderate Alzheimer's disease in this population, although the sample size of this study was too small for statistical significance	Problems included obtaining ethical approval (>1 year), recruiting sufficient numbers of patients to detect statistically significant differences, high incidence of co-morbidity and concern over consent/assent for people with learning disabilities
Treatment completers from Prasher 2002 trial (N=27) NS	Dementia Scale for Mentally Retarded Persons (DMR), Severe Impairment Battery (SIB), Neuropsychiatric Inventory (NPI), Adaptive Behaviour Scale (ABS) No	Non-random allocation for open label study (quasi-experimental study). Change scores relative to baseline enrolment	There is significantly less deterioration in global functioning and adaptive behaviour in DS adults with Alzheimer's disease treated with donepezil compared to a matched non-treated group over a two-year period	Conclusions based on a subgroup of 13 patients (AOD + NOD)

Author	**Study design** **Study duration** **N enrolled**	**Setting** **Blinding**	***Classification*[8]** **Principal rationale[9]**	**Interventions**	
(Schneider *et al.*, 2003)	RCT, double-blind, placebo-controlled 8 weeks 747	US 66-site study Double blind	*Investigation of drug in new patient populations* To establish the effect size of SSRIs in elderly patients with depression.	Sertraline, 50 mg OD or BD Placebo OD	

	Inclusion criteria **Exclusion criteria**	**Outcome measures** **Costs included**	**Study Characteristics**	**Main findings**	**Comments**
	Outpatients aged >60 with DSM-IV diagnosis of major depressive disorder Concurrent psychosis, dementia, current/past history of psychosis or bipolar disorder; substance abuse (<6 mths); concomitant use of CNS drugs or psychotherapy	Hamilton depression scale, Clinical Global Impression (CGI) severity rating, CGI improvement scale, Patient Global Impression, MMSE, Quality of Life Enjoyment and Satisfaction Questionnaire, SF-36. Safety and compliance also assessed No	No significant baseline differences between groups. Mean age 70, 93% Caucasian and almost 90% taking concomitant medicines (mean: 5), No significant between-group differences in HRQOL measures	Sertraline was effective and well tolerated by older adults with major depression, although the drug-placebo difference was not large in this 8-week trial	There are few placebo-controlled trials of SSRIs in this patient population Patients were severely depressed and suffered from high levels of co-morbidity

4.1.3 Ongoing post-launch studies in the UK

Three examples of ongoing post-launch studies of pharmaceuticals are discussed, covering the rationale and background to the study, funding arrangements and issues arising. We also consider whether the study could have been undertaken pre-launch.

4.1.3.1 Cohort study of drugs for Multiple Sclerosis

The post-launch longitudinal study of drug treatments for Multiple Sclerosis (MS), which incorporates a risk-sharing agreement, emerged from a 'negative' NICE appraisal decision. Published in January 2002, the NICE appraisal of treatments for Multiple Sclerosis (No. 32) found no basis for recommending the drugs as cost-effective for routine use, although patients already receiving these treatments were to continue as clinically appropriate (National Institute for Clinical Excellence, 2002)(§1.2) with Trusts and health authorities collecting data on this group of patients (§5.1). NICE also encouraged the manufacturers, the Department of Health (England) and the National Assembly for Wales to "usefully consider what actions could be taken, jointly" (§7.1) to explore how any or all of the drugs could be secured for patients in a cost-effective way.

In February 2002, the Department of Health (together with their Scottish, Welsh and Northern Irish counterparts), the manufacturers and patient bodies agreed on "a unique 'payment by results' agreement" (Department of Health, 2002d). Eligible patients would be assessed by a specialist neurologist and then prescribed the drug "most likely to be clinically effective for them" (Department of Health, 2002d). Detailed monitoring of patients at baseline and annually thereafter would assess each patient's progress.

Funding of the scheme involved a partnership. The NHS would pay for the drugs, with health authorities and primary care trusts operating under a statutory obligation to fund the treatments (Department of Health, 2002a). In practice, the drug price paid by the NHS was discounted by between 6% and 26% (Anonymous, 2002),

with the total cost to the NHS for the MS drugs therefore amounting to around £50m annually (Sudlow and Counsell, 2003). Manufacturers and the Multiple Sclerosis Society committed to helping fund some of the 21 additional specialist nurses, additional consultant sessions and other clinical and administrative posts needed to implement the scheme (Department of Health, 2002b).

Under the agreement, target outcomes were agreed for each drug and drug prices to the NHS would be adjusted 'according to whether expected patient benefits are realised' (Department of Health, 2002d), with a view to achieving a cost-effectiveness threshold of £36,000 per quality-adjusted-life-year over a twenty year period (Sudlow and Counsell, 2003). In principal, this meant that prices could go up as well as down (Cooper *et al.*, 2005). Outcomes data would be owned by the Multiple Sclerosis Trust (Anonymous, 2002) and actual performance was to be compared with expected disease progression, based on the natural history of the disease as documented by a Canadian cohort study from the 1970s and 1980s (Department of Health, 2002a, Warlow, 2003). The study was therefore quasi-experimental in design, comparing the treatment groups with notional historical controls. The rationale for selecting a quasi-experimental design in preference to a randomised trial was that the scheme was intended to assess cost effectiveness, and was not to be seen as a further 'clinical' trial of efficacy (Department of Health, 2002a). As licensing decisions require evidence from RCTs, this type of study could not have been done pre-launch. Although the UK health departments assumed that the existing clinical evidence was valid, others questioned its quality and argued that an independently conducted, pragmatic RCT would deliver more robust (reliable and unbiased) findings than those from a quasi-experimental study (Sudlow and Counsell, 2003, Warlow, 2003). Section 4.1.4 addresses some of these methodological issues in more depth.

The Department of Health published a health service circular, stating that up to 9,000 patients were expected to participate in the risk-sharing scheme, representing about 12.5% to 15% of MS sufferers in the UK (Department of Health, 2002a). The scheme was intended to run for 10 years, with patients followed up irrespective of

whether treatment was continued (Cooper *et al.*, 2005). Prescribing began in May 2002, with recruitment from October in the same year. The study faced practical problems: progress was initially slower than expected and there were reports that clinicians were unclear about how the scheme was meant to operate (Polak, 2002). Nevertheless, 3000 patients had been recruited by the end of the first study year (Multiple Sclerosis Trust, 2003). Recruitment closed in April 2005, with a total of 5400 patients enrolled from 70 UK centres. These patients were mostly female (75%) and suffering from the relapsing remitting form of the disease (83%) (Cooper *et al.*, 2005). The current estimate of total exposure to the MS drugs is around 14% of the 70,000 MS sufferers in the UK, which includes those receiving treatment prior to the study, study patients and those treated during the study period, but who declined consent to be monitored. The first study findings will be based on the interim cost analysis which is due in April 2007.[10]

4.1.3.2 SANAD for epilepsy

During the 1990s, four new antiepileptic drugs were introduced into the UK. The new drugs had been licensed on the basis of placebo-controlled 'add-on' trials and meta-analysis had suggested there were differences between the drugs that needed to be clarified by head-to-head trials (Chadwick, 2000). Although some trials comparing the new drugs with carbamazepine (an older drug) existed, the trials were short-term, failed to report relevant outcomes and did not assess cost-effectiveness. The existing evidence on the new drugs was therefore insufficient to inform clinical practice. The SANAD (Standard And New Antiepileptic Drugs) trial is a pragmatic, open, randomised study comparing longer-term clinical outcomes (including tolerability and quality of life) and cost effectiveness of standard and new antiepileptic drugs. The principal aim of the study is to determine the appropriate position of the new drugs in the treatment sequence, although the economic evaluation is also important in determining the cost implications for the NHS.[11]

Only patients for whom monotherapy represents the best therapeutic option are eligible for inclusion in the trial. Patients, comprising both

[10] Personal communication from MSS study clinical co-ordinator, 03/10/05

[11] http://www.ncl.ac.uk/pahs/research/services/technology/chronic/sanad.htm accessed 24/11/05

children (aged five or above) and adults, are randomised to one of two arms. In one arm of the trial, patients receive a standard drug treatment (carbamazepine or sodium valproate), whilst in the other arm, patients receive one of the new antiepileptic drugs: lamotrigine, gabapentin, topiramate or oxcarbazepine. The clinicians choose the appropriate dosage and, for patients in the standard drug arm of the trial, also select which of the two drugs patients are to receive. Outcome measures include seizure recurrence, psychosocial handicap and time to remission (Chadwick, 2000).

Funded by the NHS Research & Development HTA Programme, recruitment at the three participating centres began in September 1998. Recruitment closed in August 2004 and the 2400 patients were followed up until August 2005, with findings due to be published in 2007.[12]

Since licences for the new drugs were granted over a period of a number of years, a pre-launch trial of all these drugs would not have been possible. However, SANAD *could* have been undertaken pre-launch with respect to some of the more recently licensed drugs.

4.1.3.3 AD2000 for Alzheimer's Disease

AD2000 was a pragmatic trial that aimed to produce reliable evidence on the value of the antidementia drug donepezil in routine practice, addressing the questions highlighted by NICE guidance on issues such as optimal dosing, treatment duration, and cost-effectiveness. Previous research had demonstrated small, but statistically significant, improvements in cognition for patients taking donepezil compared with those taking placebo (Schneider, 2004). However, the research had failed to demonstrate long-term effectiveness, or to show that the drug reverses the underlying disease process. The impact of the drug on day-to-day functioning, behavioural disturbance, and the quality of life of both the patient and their carer was also unclear.[13] Furthermore, previous trials had high levels of dropout, due to adverse events, which resulted in missing outcomes data. This could potentially bias overstate) estimates of effect size. The AD2000 trial had

[12] http://www.ncchta.org/project.asp?PjtId=1031 accessed 24/11/05

[13] http://www.ad2000.bham.ac.uk/trial/ accessed 24/11/05

comparatively little missing data and used sensitivity analysis to test the robustness of its findings.

The trial was run by the University of Birmingham Clinical Trials Unit and funded by the West Midlands NHS Research and Development Executive. The manufacturers were not involved in the study beyond supplying the drug on a commercial basis.

AD2000 recruited 565 people with mild or moderate Alzheimer's disease who were randomly allocated either donepezil (5mg daily) or placebo (AD2000 Collaborative Group, 2004). After a 12-week run-in period, patients were re-randomised to either donepezil (5mg or 10 mg daily) or placebo, for as long as was clinically appropriate. Primary outcomes included institutionalisation and progression of disability; secondary outcomes included cognition measured by the mini-mental state examination (MMSE), functional ability, behavioural and psychological symptoms, psychological well-being of the carer, death, safety and compliance. Outcomes data were analysed on an intention-to-treat basis, which gives a pragmatic estimate of benefit and requires outcomes data for all randomised subjects (Hollis and Campbell, 1999). The economic evaluation adopted a societal perspective and assessed the incremental costs associated with treatment as well as the cost effectiveness of donepezil in terms of cost per day of high-level disability averted.

In order to provide robust estimates of effectiveness and cost-effectiveness, AD2000 aimed to recruit around 3000 patients. However, when NICE guidance on the antidementia drugs was published in January 2001, many centres switched to open-label NHS prescribing. This affected recruitment and the trial analysis, with the need to censor all data for patients at these centres in order to avoid biased estimates (AD2000 Collaborative Group, 2004). Although the triallists estimate that with 482 patients entering the long-term phase of the trial this provided 90% power to detect a 6-month delay in institutionalisation (Gray *et al.*, 2004), the low levels of recruitment have been criticised for potentially producing a false negative result (Akintade *et al.*, 2004). The study was not included in the metra analysis undertaken as part of the 2005 review of Alzheimer's drugs

conducted by SHTAC for NICE (Coveman *et al.*, 2004).

The recruitment difficulties encountered once the anti-dementia drugs became available on the NHS suggest that it may, in some respects, have been easier to conduct the trial pre-launch. However, since the trial was intended to assess longer-term outcomes, a pre-launch design would have delayed the widespread availability of the drugs and may therefore not have been socially efficient: it may not have offered the manufacturers enough of an incentive and would have been likely to face opposition from patient groups and clinicians. From a value of information approach, phase III and related data can inform the decision to reimburse (or not reimburse) the product, with longer-term data being collected subsequently.

4.1.4 Post-launch study design: methodological strengths and weaknesses

Table 6 presents a summary of the strengths and weaknesses associated with different study designs (definitions of the different study designs are in Table 3).

Table 6: **Strengths and weaknesses of study designs used in post-launch research**

Study Design	Strengths	Weaknesses
RCTs (explanatory)	Controls for known, measured, unknown and unmeasured confounders	Gives little indication of 'real world' effectiveness i.e. external validity may be weak
	Estimates of efficacy are robust; i.e. internal validity may be strong	Can be expensive to conduct especially if longer duration
	Usually double-blinded, protecting against performance bias[14] and detection bias[15] Concealment of treatment allocation[16] protects against selection bias[17]	
	Has the potential to detect small differences in outcomes (small effect sizes)	
	Hawthorne effect should be similar in both groups[18]	
RCTs (pragmatic)	Controls for known, measured, unknown and unmeasured confounders	Findings of effectiveness or cost may be difficult to generalise to other pragamatic settings
	Estimates of effectiveness robust within trial setting	Can be expensive to conduct, especially if longer term
	Cost (resource use) data help inform policy decisions	Double blinding not always possible
	Assessor blinding an option Has the potential to detect small differences in outcomes, but in real world context	
	Hawthorne effect should be similar in both groups[18]	
Non-randomised comparisions	Allows comparison of products that are not be amenable to randomisation for ethical or practical reasons	Difficult to allow for all known confounders and impossible to account for unknown or unmeasured confounders
	Often less expensive to conduct than randomised trials Has the potential to detect large differences in outcomes (large effect sizes)	Hawthorne effect may arise in prospective studies[18]

Sources: (Clarke and Oxman, 2003, Khan *et al*., 2001)

[14] Performance bias refers to systematic differences between comparison and intervention groups in terms of the care provided (other than the intervention itself)

[15] Detection bias refers to systematic differences between comparison and intervention groups in terms of outcome assessment

[16] However, many RCTs do not adequately conceal treatment allocation.

[17] Selection bias refers to systematic differences between comparison and intervention groups in terms selection process

Any controlled prospective study may suffer from attrition bias, which occurs when there are systematic differences between withdrawal rates between the intervention and comparison groups. The methods by which the loss of study participants is handled in the analysis can bias the results. Uncontrolled studies, such as case series or cohort studies, may enable an association between an outcome measure and an intervention to be identified. The reliability of the attribution of the outcome to the intervention depends on having sufficient data on known confounding factors, although unknown biases cannot be ruled out or accounted for.

The case studies presented in Table 5 provide some practical illustrations of the strengths and weaknesses associated with different study designs. Several of the studies identified benefits for the products scrutinized (Condemi *et al.*, 1997, Ascher-Svanum *et al.*, 2004, Schneider et al., 2003). However, these studies also provided evidence about limitations and side effects. For example, a randomised trial comparing two inhaled corticosteroids demonstrated that one was more efficacious, but also that this product was associated with a higher incidence of oral candidiasis (although the authors did not report whether this was significantly higher than for the active comparator) (Condemi *et al.*, 1997). The study of elderly depressed patients demonstrated that the antidepressant under scrutiny was superior to placebo, but also noted that the difference was small (Schneider *et al.*, 2003). This study illustrates why certain patient groups – particularly those that are typically excluded from licensing RCTs – may be difficult to research. The researchers selected patients with major depressive illness; many of the patients suffered considerable levels of co-morbidity and were taking on average five additional medicines. It is therefore perhaps unsurprising that an eight-week trial of an antidepressant had little clinical effect. Similar problems were encountered in the studies by Prasher and colleagues (Prasher *et al.*, 2002, Prasher *et al.*, 2003). Attempting to examine the impact of an anti-dementia drug in patients with Down's syndrome, the triallists encountered considerable difficulties in obtaining ethical approval, in achieving satisfactory informed consent /assent and in recruiting sufficient patient numbers, despite the high prevalence of

[18] The Hawthorne effect means that measuring or observing behaviour will usually disturb that behaviour

dementia in this patient group. The HERS trial, a large RCT of hormone replacement therapy (HRT) in postmenopausal women with established coronary heart disease, demonstrated a reduced incidence of diabetes associated with active treatment. However, the trial also showed no impact on secondary prevention of CHD (Herrington, 1999), and an increased risk of venous thromboembolism (Grady *et al.*, 2000). For this reason, the positive impact on diabetes incidence was insufficient to recommend routine use of the drug in this patient group.

Various methodological issues associated with the UK Multiple Sclerosis scheme (section 4.1.3.1) have been raised, although these are not directly related to the *risk-sharing* character of the study, but to other factors. For example, concerns were expressed about the practical and scientific feasibility of the scheme (Warlow, 2003). With fewer than 400 consultant neurologists in the UK, the task of assessing patients for eligibility, and counselling those who turn out to be ineligible, appeared unfeasible. Other criticisms have been levied, such as: the outcome measure used to determine drug performance was flawed and the study design – a cohort study with historical controls – open to bias; there were deficiencies in the trial data informing the economic model (from which the cost per QALY threshold was derived); the omission of another comparator drug, azathioprine; inadequate follow up of non-responders; and the use of unblinded outcomes assessment (Sudlow and Counsell, 2003). Calls for independently conducted RCTs ensued (Sudlow and Counsell, 2003, Warlow, 2003). Whilst some of these criticisms were countered by the scheme's scientific advisors (Chadwick and Gray, 2003), it appears that the Multiple Sclerosis scheme endorsed these treatments as legitimate prescribing options, with the consequence that plans to conduct an independent RCT were quashed (Warlow, 2003, Chadwick and Gray, 2003). Nevertheless, the MS Trust welcomed the scheme, taking a longer term perspective on the potential benefits to patients that could result from the improved infrastructure, staffing and higher public awareness accorded to the condition by the scheme (Multiple Sclerosis Trust, 2003).

CHAPTER 5 – WHAT ARE THE PROBLEMS AND LIMITATIONS IN UNDERTAKING POST-LAUNCH STUDIES?

Methodological barriers relating to study design constitute just one of the barriers faced by those undertaking post-launch studies. We asked Global Heads of outcomes research about their views on such barriers. Respondents were asked to indicate which barriers were associated with certain types of study design; the option of specifying additional barriers and / or additional study designs was also given.

5.1.1 Findings from the survey of Global Heads of outcomes research

We asked Global Heads of outcomes research about their perceptions of the obstacles facing them when undertaking post-launch research (Table 7 overleaf). In the survey of UK heads, the question was product-specific and so findings from the two surveys are reported separately.

Table 7 **Obstacles to undertaking post-launch studies: survey of Global Heads, 2004**

	Ethical restrictions	Logistics/ organisational issues	Overall cost/study duration	
RCTs (explanatory) against other competitor products		■	■■■	
RCTs (pragmatic), also collecting economic data		■	■■■	
Non-randomised comparisons		■	■	
Administrative database analyses		■		
Clinical case series		■		
Free standing empirical studies			■	

Key

■■■■ Cited by at least 80% of respondents

■■■ Cited by ≤ 79% and > 60% of respondents

■■ Cited by ≤ 59% and > 40% of respondents

■ Cited by ≤ 39% and > 20% of respondents

Cited by under 20% of respondents

	Negotiations over study funding	Risk/benefit for the company	Payer/ authority disinterest	Methodological issues
		■■■■		
	■	■■	■	■■■
		■	■■	■■■
			■	■■
	■		■	■
	■		■	■

The balance of risks and benefit to the company was seen as an obstacle associated with conducting explanatory RCTs against competitor products (89% of respondents; N=18) as well as with pragmatic RCTs (56%). The overall cost and/or study duration for these types of trial was another important barrier to post-launch research, cited by 78% and 61% of respondents for explanatory and pragmatic RCTs respectively. Methodological factors were highlighted as problematic for pragmatic RCTs (61%), non-randomised comparisons (61%) and analyses of administrative databases (44%). Although we invited respondents to suggest other barriers and additional study designs, none of the respondents did so.

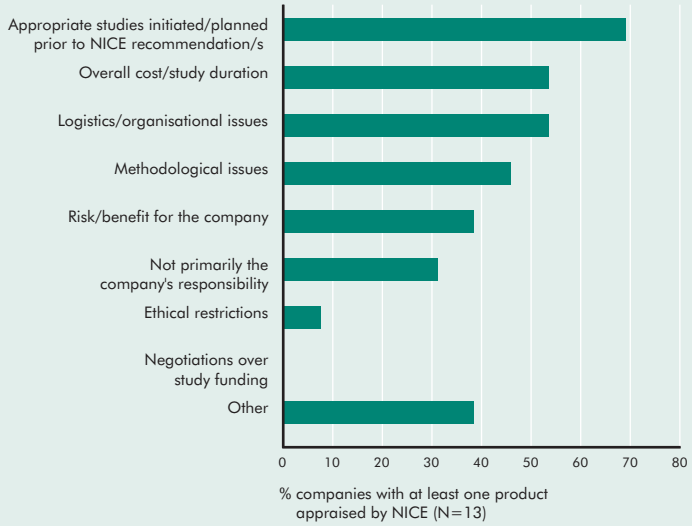
In France, the pharmaceutical industry and the government have agreed that the cost of post-launch studies must be "reasonable", that is, proportionate to expected sales of the product,[7] which explicitly recognises the balance of costs and benefits faced by those who fund further research.

5.1.2 Findings from the survey of UK Heads of outcomes research

We asked UK respondents why their companies had made no direct response to NICE recommendations for further research on a particular product (Figure 5). This question was relevant for thirteen of our fourteen respondents, as one company had not had a product appraised by NICE (see Appendix, Table 9).

Around seven out of ten companies indicated that they did not respond to NICE guidance because they had already planned or initiated appropriate studies prior to NICE guidance. Cost, logistical and methodological issues were important barriers for around half of our respondents. We also invited companies to specify their own reasons for not responding directly to NICE recommendations. One respondent observed that NICE recommendations were out of line with the company's marketing strategy and said that the company had already initiated its own large observational studies. Another cited imminent patent expiry date as a reason for lack of action. The lack of shorter-

Figure 5: **Reasons why companies made no direct response to NICE recommendations for further research: survey of UK Heads, 2004**



term benefit coupled with the longer-term high cost commitment, and the opportunity cost of investing in research and development for this drug rather than others in the company's portfolio were noted:

> Whilst such recommendations may be appropriate for a newly launched product … it's difficult to justify the investment of such resources in a mature product when these resources are needed elsewhere (i.e. in R&D).

Only one company disagreed with all NICE recommendations for its product, but eight of the thirteen responding companies disagreed with some. Methodological objections included the interpretation of clinical outcome measures and the "NICE obsession" with randomised trials. Issues also highlighted included the inadequacy of the recommended study duration, the perceived irrelevance of some recommendations and the lack of recognition of the feasibility of studies – "the economics of acquiring new evidence" – particularly for

out-of-patent drugs. In making recommendations for further research, NICE rarely specifies who should carry out or fund the work. However, this response does suggest that consideration should be given either to improving the incentive to manufacturers or to the use of public funds to address NICE's data needs. The latter is currently within the remit of the NHS Health Technology Assessment Programme.

CHAPTER 6 – HOW CAN THE RANGE AND QUALITY OF POST-LAUNCH STUDIES BE IMPROVED?

Assessing the expected value of obtaining additional information can help to determine the cost-effectiveness of post-launch research for society, payers or manufacturers (Claxton, 1999, Claxton *et al.*, 2002). The 'value for information approach' involves determining if the expected benefits exceed the expected costs of additional information, with the type of technology and its application important factors:

> Efficient regulation would demand more information for some new technologies as compared to others and require different amounts of information for the same technology in different circumstances (Claxton, 1999).

There are essentially two approaches that might improve the quality and range of post-launch studies. Firstly, provided there is already good quality evidence for treatment effect, economic studies could be made easier and less costly to undertake by (i) relaxing the methodological requirements stipulated by payers and reimbursement agencies, or (ii) improving access to existing databases of longitudinal data or (iii) setting up new databases. Secondly, the balance between the incentives and disincentives of undertaking research could be addressed by considering issues such as funding responsibility, outcome agreements, conditional reimbursement and risk-sharing.

6.1 Towards a more pragmatic approach

Methodological requirements were clearly seen as a barrier by some companies, and there appears to be a trade-off between cost, design and the value of information generated by research. Reducing methodological requirements may encourage post-launch research by altering the balance of costs and benefits for those funding the research. A value of information analysis, by assessing the probability that particular methodologies would be cost-effective, can help inform recommendations or requirements by decision-makers. One approach is to place less emphasis on randomised designs.

It is clear from our surveys that companies do conduct randomised trials post-launch, although the extent of this varies between

[19] One of the fourteen respondents had not had a product appraised by NICE and so was not asked the question.

companies and by product. It is unclear whether this is related to an explicit or implicit requirement by reimbursement agencies or payers, and therefore whether relaxing these requirements would encourage other types of post-launch research.

However, it seems that reimbursement agency recommendations for randomised trials are less common than might be thought. When we analysed NICE recommendations for further research, we found that just 28% of appraisals specified that a randomised controlled trial was required (Table 2). The survey of five European reimbursement agencies supported this finding: when recommending post-launch research, all agencies regularly or sometimes sought 'real world' data and none routinely required the use of randomised trials to obtain this data. Only one European reimbursement agency believed that less emphasis on randomised designs would encourage post-launch research; two respondents disagreed and two were undecided. When we asked Global and UK Heads of outcomes research if relaxing requirements for randomised trials would encourage post-launch studies to be undertaken, opinion was again divided but more respondents from both surveys agreed (42%) than disagreed (29%). Methodological issues, such as determining sample size, choice of comparator and devising long-term follow-up, were perceived by Global Heads to be a greater problem for pragmatic RCTs (61%) than explanatory RCTs (11%) (see Table 7). Almost half (46%) of the respondents to the survey of UK Heads said that methodological issues had been a reason why their companies had taken no action in response to NICE recommendations for further research (see Figure 5).

6.2 Use of longitudinal databases

To further facilitate post-launch research, particularly where 'real world' data are required, access to databases of *longitudinal* data, which track patients over time, could be improved and the existing infrastructure enhanced by investing in new databases. Guidelines on the retrospective use of such databases for outcomes research have been

drawn up (Motheral *et al.*, 2003) and the potential of such databases to explore pharmacoeconomic questions post-launch has been recognised (Silman *et al.*, 2003).

A review of routine databases identified 272 databases in the UK, of which 62 (23%) were deemed to be potentially useful for health technology assessment (HTA) (Raftery *et al.*, 2005). NHS funding for databases was chiefly focussed on those needed for managerial purposes, but these databases were not considered to be useful for HTA. Table 9 describes a selection of longitudinal databases in the UK.

One of the earliest UK databases was established in 1977 by the Society of Cardiothoracic Surgeons of Great Britain and Ireland (SCTS). Cardiac surgeons voluntarily submitted their annual figures to the United Kingdom Cardiac Surgery Register (Treasure, 1998). The register was seen as a useful benchmark against which to discuss variations in the provision of services and for individual surgeons to monitor their own mortality figures against a national average. Despite the existence both of this register and of Hospital Episode Statistics, the high-profile cases of unacceptable mortality for paediatric cardiac surgery at Bristol Royal Infirmary were not detected for almost ten years (Aylin *et al.*, 2004). The Central Cardiac Audit Database (CCAD) now covers a range of cardiothoracic procedures for adults and children and incorporates data collected by the SCTS. These data are linked to the Office of National Statistics (ONS) to enable mortality tracking. The National Clinical Audit Support Programme, introduced to support the implementation of National Service Frameworks, includes coronary heart disease (CHD), but also covers non-surgical treatments. In addition, data are collected on cancer, diabetes and mental heath (Department of Health, 2002c). The British Rheumatology Society has set up the Biologics Registry with the help of pharmaceutical industry funding. Like the CCAD, the Registry uses ONS data but tracks new cases of cancer as well as mortality. Outcomes data are also collected directly from patients and rheumatologists (Silman *et al.*, 2003). Established in 1987, the General Practice Research Database (GPRD) is reputed to be the

world's largest computerised database of primary care records (Table 9) and has been widely used to address a variety of research questions, including the long term health benefits of a drug post-launch (Bradbury *et al.*, 2005).

European countries operating insurance-based health care have claims databases that could be used for pharmacoeconomics and outcomes research. For example, France has the 'Assurance Maladie' (sickness insurance) with data held in the SNIIR-RM (Système National d'Informations Inter-Régimes de L'Assurance Maladie) which includes anonymised patient-level reimbursement data from all the French sickness funds (Le Gales *et al.*, 2003).

Raftery and colleagues note that routine databases offer great potential for health technology assessment and recommend that closer policy links be forged between routine data and research and development (Raftery *et al.*, 2005). As part of the drive to modernise NHS information technology, electronic patient records have been developed. These could lead to new electronic networks, linking different databases and enabling patient pathways to be tracked both longitudinally and between NHS organisations and across disease areas. This could, in principal, greatly facilitate post-launch research (Department of Health, 1999).

Table 8 **A selection of longitudinal databases in the UK, 2005**

Name of Database **Date established**	**Rationale**	**Population**	**Country** **Funding source**	
British Society for Rheumatology Biologics Register (BSRBR) (Silman *et al.*, 2003) January 2002	To monitor the long-term safety of biologic agents To collect control data from a large group of people not treated with biologics, but with similar disease severity to those being monitored on the register. There are currently seven control centres operating across the UK (Silman *et al.*, 2003)	Consenting patients with rheumatic diseases treated with biologics Consenting patients with rheumatic diseases starting or changing to a new disease modifying anti-rheumatic drug (DMARD)	UK 'Relevant' pharmaceutical companies	
Central Cardiac Audit Database (CCAD)[21] 1996	To collect patient specific data relating to cardiac interventions and major clinical events	Patients with cardiovascular disease Ablation treatment for arrhythmias adult cardiac surgery coronary angioplasty heart and lung transplantation implanted pacemakers/ implantable cardiac defibrillators myocardial infarction procedures carried out for congenital cardiac defects	UK Publicly funded	

[22] http://www.rheumatology.org.uk/ (accessed 24/11/05)
[21] http://www.ccad.org.uk/ (accessed 24/11/05)
[22] http://www.lshtm.ac.uk/docdat/records.php?t=records&id=PAEDS (accessed 24/11/05)

	Data collected/ monitored	Access	Comments
	Disease severity; disease duration; adverse events (e.g. serious infections); hospitalisation; surgery	Pharmaceutical companies have access to data on their own product(s)	Described as "ground-breaking" it is the only study of its kind in Europe[20] Linked with ONS mortality/cancer data
	Incorporates several databases each collecting its own dataset	Hospitals can purchase a licence to access the database(s) Summary reports available free of charge on the website	Hosted by the NHS Health & Social Care Information Centre (HSCIC) Longitudinal tracking of outcome possible by linking records across hospitals and with the Office of National Statistics See also National Adult Cardiac Surgical Database (NACSD) and Paediatric Cardiac Procedures Database (PAEDS)[22]

Name of Database Date established	Rationale	Population	Country Funding source	
General Practice Research Database (GPRD) June 1987	To promote and protect public health[23]	Patients registered in participating general practices Reputed to be "the world's largest database of anonymised longitudinal medical records from primary care"[23]	UK VAMP Ltd provided initial funding for the database. The Medicines Control Agency funded the set-up costs of GPRD, which is now managed by the Medicines and Healthcare products Regulatory Agency Access charges	
Health Outcomes Data Repository (HODaR)[25]	To provide timely, comprehensive and cost effective health outcomes data to various users	All discharged patients and a sample of out-patients attending a large NHS Trust	UK Access charges	
Hospital Episode Statistics data-base (HES) 1987	Replaced Hospital Activity Analysis scheme, used for contracting in the internal market in the 1990s	All admitted patients treated in NHS hospitals in England[26] Recent expansion to include all NHS outpatient and A&E attendances[27]	England[28] Publicly funded Access charges for some data	

[23] http://www.gprd.com/whygprd/ (accessed 24/11/05)
[24] http://www.lshtm.ac.uk/docdat/records.php?t=records&id=GPRD (accessed 24/11/05)
[25] http://www.crc-limited.co.uk/index.html (accessed 24/11/05)
[26] http://www.lshtm.ac.uk/docdat/records.php?t=records&id=HES (accessed 24/11/05)
[27] http://www.statistics.gov.uk/STATBASE/Source.asp?vlnk=305&More=Y (accessed 24/11/05)

	Data collected/ monitored	Access	Comments
	Practice and patient registration details; demographics, including age and sex of patient; medical diagnosis; all prescriptions, including repeats; events leading to withdrawal of a drug or treatment; referrals to specialists and hospitals; treatment outcomes including hospital discharge reports; miscellaneous patient care information (e.g. smoking status, height, weight, immunisations, lab results)[24]	Users pay a fee to access the database, according to the amount and type of data required	Formerly known as the VAMP Research Databank Approximately 2000 doctors from 300 self-selected GP practices contribute data to GPRD 5% of UK population included but GPs self-select
	Inpatient and outpatient Quality of Life (QoL), cost and clinical information (such as biochemistry and haematology), drug and resource use across all disease groups	Subscription payable, depending on data requirements	Includes survey data and routine data
	Each record contains a variety of administrative, clinical and patient information describing the care and treatment a patient received whilst in hospital	HES publishes standard tables of analyses of NHS admitted patient care by diagnosis, operation, Healthcare Resource Group, consultant speciality, NHS Trust and Health Authority on their website. Users can also request specialised analyses to be performed on their behalf by the HES team	Hosted by Health & Social Care Information Centre (HSCIC) The data are captured from hospital patient administration systems, and HES now collects 12 million records per year from all hospital trusts in England

Name of Database **Date established**	**Rationale**	**Population**	**Country** **Funding source**	
National Adult Cardiac Surgical Database (NACSD) 1994	Quality assessment and equity of provision	All adults in NHS hospitals undergoing cardiac surgery (patients in independent hospitals excluded)	UK Publicly funded	
Paediatric Cardiac Procedures Database (PAEDS)[22] March 2000	Response to the Bristol tragedy	Procedures carried out for congenital cardiac defects	UK Publicly funded	
The United Kingdom Association of Cancer Registries 1960s[29]	Public health surveillance and health protection	National and regional information about cancer incidenct	UK Publicly funded	

[29] http://www.ukacr.org.uk/ (accessed 24/11/05)

	Data collected/ monitored	Access	Comments
	Annual cardiac surgical activity and mortality data from each NHS cardiothoracic surgical unit. The unit based data are then aggregated into an annual report providing information on cardiac surgery activity		Part of the Central Cardiac Audit Database (CCAD)
	administrative information; condition; intervention; short term outcome; major known confounders; long term outcome		Part of the Central Cardiac Audit Database (CCAD) Linked to Office for National Statistics (ONS) Mortality Data
	Person: Name, Sex, DoB, Address, Postcode, GP, NHS Number Tumour: site, morphology, behaviour, date and basis of diagnosis, extent of disease Management: hospital, consultant, treatment and referral details Outcome: survival, causes and date of death	Access to local registries through NHSNet Summary statistics available free on the Office of National Statistics website	Includes 8 English regional registries, plus registries for Scotland, Wales and Northern Ireland

6.3 Changing the balance of incentives and disincentives

Greater emphasis on nonrandomised studies or improving access to databases are just two options for changing the balance of costs and benefits for undertaking research post-launch. Others relate to the arrangements for funding studies, the actions of competitors, and the likely consequences, in terms of decision making. This section reports findings from our surveys of reimbursement agencies and pharmaceutical manufacturers (see Appendix, section #10.1.4).

6.3.1 Sharing of costs by the authorities and payers

Mixed views were expressed by respondents to the European reimbursement agency survey when asked whether they thought that authorities or payers sharing costs would encourage post-launch research. Of the five respondents, one strongly disagreed, two were neutral and two agreed – none strongly agreed. However, the pharmaceutical company respondents were more positive about the potential for cost-sharing to encourage research post-launch, with 70% of respondents agreeing that cost sharing was an incentive.

In the UK, NICE makes recommendations for further research but bears none of the cost of implementation. With its technology assessments focussed on direct health and social care costs, NICE adopts a governmental, rather than a societal, perspective when making recommendations and so costs incurred by independent organisations are not considered. Recommendations may therefore not reflect an efficient use of society's resources; even if the recommendations were efficient, the incentives for manufacturers and other independent organisations to respond positively are not apparent. However, NICE recommendations may inform calls for further research by public programmes.

An example of a cost-sharing trial is the MRC/BHF Heart Protection Study (Collins et al., 2004). This large study, which involved 69 hospitals throughout the UK, was run by the Clinical Trial Service Unit (CTSU) at the University of Oxford. CTSU designed the study

and analysed the data independently of the sponsors. Funding was provided from four sources: the Medical Research Council (MRC), the British Heart Foundation (BHF) and the pharmaceutical companies Merck & Co Inc (manufacturer of the study statin) and Roche Vitamins Ltd. The funding was provided in the form of grants, so that the pharmaceutical sponsors had no influence over how the money was spent, the day-to-day running of the study, the analysis of the data, or the presentation, publication or publicising of results.[30]

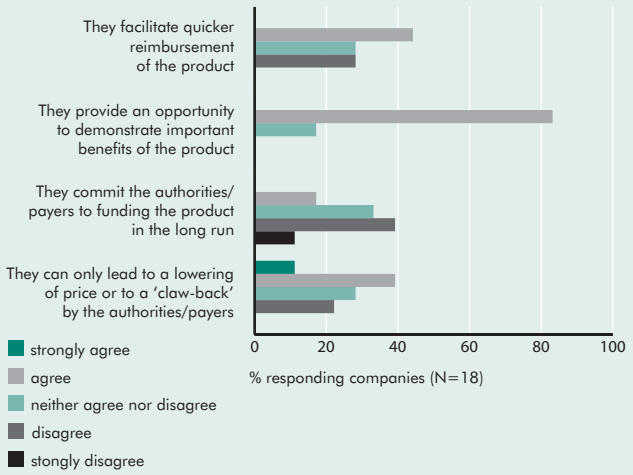
6.3.2 Linking post-launch studies with risk-sharing schemes

Just one respondent in the survey of five European reimbursement agencies disagreed that risk-sharing schemes could encourage post-launch research. Two respondents agreed that these schemes could incentivise further research. Half of our respondents (54%) to the surveys of Global and UK Heads agreed that risk-sharing would encourage research, with a larger proportion undecided (28%) than disagreeing (18%).

We also asked Global Heads of outcomes research in pharmaceutical companies about their views on the potential benefits of risk-sharing agreements (Figure 6) (the question was not addressed to UK Heads). Most of the 18 respondents (83%) agreed that risk-sharing schemes provide an opportunity to demonstrate important benefits of the product. However, half of our respondents agreed or strongly agreed that there was a danger that risk-sharing could lead to a lowering of price or to a 'claw-back' by the authorities and payers. Opinion was divided over whether these schemes commit the authorities / payers to funding the product in the long run. One respondent observed that the schemes are contractually difficult and that there is a need to agree validation parameters. Another respondent believed that these schemes increase the risk for the company and would therefore limit research and development activities to "strong" products.

[30] http://www.ctsu.ox.ac.uk/~hps/June02QandA.shtml accessed 24/11/05

Figure 6: **Respondents views on risk-sharing agreements: survey of Global Heads, 2004**



6.3.3 More studies being undertaken by competitors

We asked Global and UK Heads of outcomes research in pharmaceutical companies whether they thought that competitors undertaking more studies would provide an incentive for post-launch research. Around three-quarters of the 25 companies responding to this question agreed (56%) or strongly agreed (18%). Strong disagreement with the statement was rare (2%).

6.3.4 Commitment to revise decisions on the basis of post-launch findings

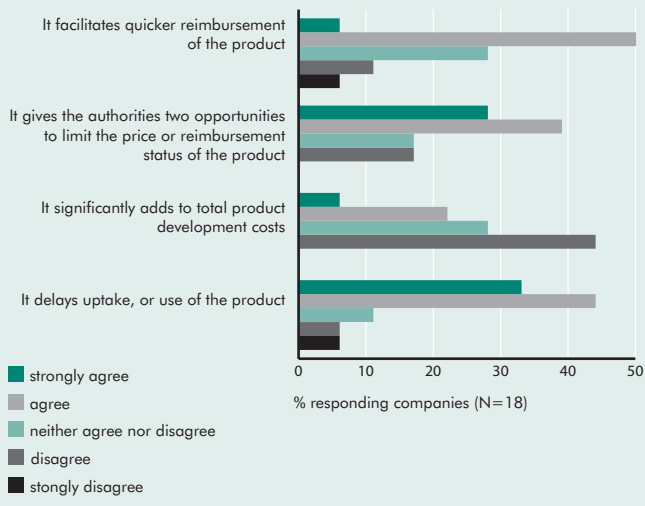
A commitment by authorities or payers to revise their decisions on the basis of post-launch research was the factor most strongly endorsed as likely to encourage post-launch research, by our European reimbursement agency respondents as well as by pharmaceutical

companies. No respondent disagreed and just 13% of company respondents gave a neutral opinion. One of the five European reimbursement agency respondents strongly agreed with this statement, as did a similar proportion of responding pharmaceutical companies (22%).

6.3.5 Conditional reimbursement

Conditional reimbursement involves linking pricing approval, or approval for use, of a drug to a requirement for further data collection, with a subsequent review in 2-3 years' time. It embodies many of the incentives and disincentives of risk sharing, but there is no formal agreement on the outcomes parameters and the precise sharing of the financial risk. We asked Global Heads of outcomes research for their views on conditional reimbursement (the question was not addressed to UK Heads). Findings are shown in Figure 7.

Figure 7: **Respondents views on the effects of conditional reimbursement: survey of Global Heads, 2004**



Two respondents listed some additional effects of conditional reimbursement. One respondent was of the view that it shifts responsibilities of the health care system onto the pharmaceutical industry (e.g. request to provide local data on the burden of disease). This respondent also felt that conditional reimbursement opens the door for unreasonable requests, because these are not informed by an assessment of the expected benefits and costs associated with this additional information. Furthermore, conditional reimbursement was perceived to take no account of the patent expiry date of the product. A second respondent believed that conditional reimbursement and post-launch studies should only be mandatory when evidence at launch is clearly inadequate. This respondent was also of the view that it would probably add further financial risk to the product profile and hence affect shareholder value. In the UK, it is worth noting that, while NICE rarely makes its decisions conditional on the need for further research, it does routinely review its decisions (usually after three years). A number of the products originally approved by NICE are now being re-appraised. It will be interesting to assess whether the re-appraisals make mention of the manufacturers' response or non-response to the recommendations for future research made first time around. Based on a recent review of the antidementia drugs, NICE has provisionally recommended that further research should focus on devising reliable methods for identifying sub-groups of people for whom the drugs are both clinically and cost-effective treatments (National Institute for Clinical Excellence, 2005). Whilst the original appraisal (No. 19) recommended research to explore whether those with severe dementia, or other forms of dementia, might benefit from the drugs, the Appraisal Consultation Document has offered a more narrowly defined research question.

6.3.6 Other issues

We invited respondents to suggest additional factors that could influence the level of post-launch research. From the survey of Global Heads, one respondent felt that post-launch research was best seen in a context of commitment to monitoring and validation as part of

united formulary contract. Another respondent pointed to the need for better methods to assess risk/benefit ratio for trials, such as risk simulations and mathematical models, and the need to utilise established 'best research practices' in designing, conducting and analysing "real-world effectiveness" studies. The ISPOR Task Force consensus statement contains some recommendations on these points (Drummond et al., 2003). UK Heads cited easier access at launch in return for research commitment by the company and linkage of costs to guaranteed outcomes as means of encouraging post-launch research.

CHAPTER 7 – CONCLUSIONS

There are four main conclusions from this research. First, economic studies undertaken post-launch have an important role in determining the true cost-effectiveness of new pharmaceuticals. Some types of studies, such as comparisons with other new products in development, or investigation of the drug under conditions of normal clinical practice, are just not feasible before the drug has approval to market. Other important studies, such as examining the efficacy of a product in the long-term, could be done prior to launch (or prior to reimbursement approval), but this would delay patient access to a potentially beneficial product and may therefore not be socially efficient. From a value of information approach, Phase III and related data can inform the decision to reimburse (or not reimburse) the product, with longer-term data collected subsequently.

Secondly, there are considerable variations in practice concerning post-launch studies. This arises partly from the fact that there is no formal requirement in any jurisdiction, and partly because companies face big challenges in designing and conducting studies. Several companies mentioned the fact that post-launch studies compete with standard clinical research for research and development funds. Therefore, in the absence of any formal requirement, there would need to be a clear commercial objective for undertaking a study. This situation may change if the payers for health care show more of an interest in post-launch studies and give a commitment to revise their decisions based on the results. In order to invest resources in undertaking studies, companies would need to be sure that their findings would be important in gaining, maintaining or expanding market access for their products.

Thirdly, it is important that post-launch studies are conducted in an efficient fashion. Therefore, prior to making requests for further research, decision-makers should consider the costs and benefits, ideally through a formal value of information analysis. In addition, the methodology of studies should be fit for purpose and it should be recognised that randomised trials, which are expensive and time-consuming to conduct, are not required to answer every question. Observational studies may often be sufficient and investments should

be made in developing, and improving access, to routine databases.

Fourthly, the responsibility for funding and conducting post-launch studies and the appropriate incentives need to be considered. Besides manufacturers, other public and private bodies can play an important role, commensurate with the incentives for undertaking further research. For example, public funding could be made available in order to answer questions that are broader than those of interest to a given manufacturer. Such questions could include determining the appropriate sequencing of a range of drugs in a clinical care pathway, or exploring general issues of adherence to medication in a given disease. In some settings, research partnerships between payers and manufacturers may be beneficial. For example, in situations where the first of a new class of drugs comes to market, both the manufacturer and payer may have an interest in assessing whether it is being used appropriately. Risk-sharing schemes represent one type of partnership, since they allow the drug to be used with the objective of exploring its real potential, although evidence to date from the UK Multiple Sclerosis scheme suggests that these may be challenging to organise. In addition, professional societies could play an important role where impartiality is required, such as in maintaining registries of patients being prescribed one of a new class of drugs. In the UK, the NHS information strategy offers the potential for new electronic networks, enabling patient pathways to be tracked both longitudinally and within or between NHS organisations. Constructive dialogue between payers, manufacturers and HTA bodies is needed to help create an efficient framework for post-launch research.

CHAPTER 8 – ACKNOWLEDGEMENTS

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CHAPTER 10 – APPENDICES

10.1 Survey methods and response rates

10.1.1 Survey of European reimbursement agencies

We explored the reasons why particular European reimbursement agencies recommend post-launch research, by analysing published recommendations (NICE, England and Wales) and by a postal survey of employees of reimbursement agencies in five countries. All five agencies responded and all commented on a draft summary for their agency (response rate: 100%).

Our reasons for selecting these five countries (England, France, Portugal, Sweden and Norway) were that they had either embraced the use of economics in reimbursement decisions, or were known to be active in promoting studies post-launch. The French respondent completed two surveys, one for the Price Committee and one for the Transparency Commission. The survey consisted of nine questions, with an invitation to participate in a telephone interview or to correspond by email. Questions covered agency characteristics; recommendations for post-launch research; agency interest in 'real-world' data and any associated study design recommendations; level of response to agency recommendations; and, as in the Global Heads survey, respondents' views on factors that could encourage post-launch research.

10.1.2 Survey of Global Heads of outcomes research

We sent surveys to 29 heads of Global Heads of pharmacoeconomics and outcomes research, including all the pharmaceutical companies in the top 20 by sales. Eighteen responses were received (response rate: 62%).

The survey comprised of nine questions, covering the motivations for undertaking post-launch research; which types of research (if any) were undertaken by the company (with examples); and the obstacles faced. Respondents were also asked which external bodies, in their experience, requested post-launch studies. Respondents' views on conditional reimbursement, risk-sharing, and factors that could encourage post-launch research, were also sought.

10.1.3 Survey of UK Heads of outcomes research

We sent surveys to the UK Heads of outcomes research in 34 companies and 14 responded (response rate: 41%). Surveys were tailored according to the number of products (if any) appraised by NICE (Table 9) and were sent by email during late November / early December 2004, with reminders sent during January 2005.

Table 9: **Survey of UK Heads of outcomes research: summary of response**

	Number surveyed	Number responding	% responding
All companies	34	14	41%
Companies with one product appraised by NICE	10	4	40%
Companies with at least two products appraised by NICE	19	9	47%
Companies with no product appraised by NICE	5	1	20%

From our analysis of NICE recommendations for further research, which covered appraisals up to and including December 2003, we matched companies with the products appraised. For companies who had had *more than two* products appraised by NICE (13/34), we developed a decision rule to select the products surveyed. Firstly, we counted the number of recommendations made for each product. Reasoning that a higher number of recommendations might be thought to increase the chance of a response, we selected products with the highest number of recommendations. Where products had an equal number of recommendations, we chose the product with the larger number of companies associated with the appraisal. Five

companies in the top 30 companies by UK sales had not had a product appraised by NICE. We therefore sent these companies a separate survey.

For companies with *two or more* NICE-appraised products (29/34), two surveys were sent. The first survey included eight questions: five questions about specific products and three 'general' questions; the second survey contained only five product-specific questions. Specific questions included company response to recommendations about the product (including the type of study undertaken); reasons why, if appropriate, no response was made; disagreement with recommendations; and examples of post-launch studies undertaken by the company. The three general questions matched those from the survey of Global Heads and covered motivations, types of study and incentives relating to post-launch research. For companies with no NICE-appraised products (5/34), the survey included six questions. This survey was identical to that used for the Global Heads, except that the questions on conditional reimbursement, risk-sharing and bodies requesting post-launch data were omitted.

10.1.4 Joint analysis of surveys from Global Heads and UK Heads

In total, 43 companies received a questionnaire for the Global Head or the UK Head of pharmacoeconomics / outcomes research, with 20 companies receiving both questionnaires. Three identical questions were addressed to both Global and UK Heads, regarding: the motivation for undertaking post-launch research (section 3.2); the types of study undertaken (section 4.1.1); and factors encouraging further post-launch research (section 6). Responses to these three questions were pooled; all other questions are reported separately. Of the 25 companies responding to the survey (response rate: 58%), there were 18 from Global Heads and 14 from UK heads, with seven companies contributing two separate responses. Mean values for these seven companies were estimated and the data reanalysed so that each company contributed a single response. Where Global and UK Heads

from the same company provided markedly different responses, these are discussed in the text.

10.2 Literature review methods

10.2.1 Identification of company-sponsored post-launch studies

As part of the survey of Global Heads and UK Heads of outcomes research, we asked respondents to provide references where details were not confidential. From both surveys, eighty references were cited, some reporting on different aspects of a single study. Within the available time constraints, a systematic review of these studies was not considered to be feasible. Furthermore, studies undertaken by non-responding companies could not be identified. We therefore decided to select particular studies for further scrutiny. To guide our study selection, we referred to the categories of recommendations made by NICE (see section 3.1.2). AM categorised the references and AM, MFD and AT reviewed and discussed which studies should be selected, bearing in the mind the sample size and study design.

10.2.2 Search process

10.2.2.1 Literature search

The literature search was undertaken to locate studies assessing the cost-effectiveness of post marketing pharmaceuticals; what part economic evaluation plays when pharmaceuticals are ready for approval, or have been approved; what types of study can occur post-launch; the methodological issues involved; who asks for this information; and what currently happens. The MEDLINE, EMBASE, CINAHL, HMIC, NHS EED and HEED databases were searched. The searches were limited by date (1996-2003) and used an economic methodological search filter. Six databases were searched (Box 1), using database-specific strategies that are listed in section 10.2.4.

Box 1 **Electronic databases searched**

MEDLINE (1996-2003/Nov week 2) (Ovid Gateway)

EMBASE (1996-2003/week 47) (Ovid Gateway)

CINAHL (1996-2003/ Nov week 2) (Ovid Gateway)

Health Management Information Consortium (HMIC) (1996-2003/11) (Ovid WebSPIRS)

NHS Economic Evaluation Database (NHS EED) (1996-2003/10) (internal CRD interface)

Health Economic Evaluations Database (HEED) (1996-2003/11) (CD-ROM)

10.2.2.2 Terminology

The terms for the search strategies were identified through discussion between an Information Officer and Health Economist, by scanning the background literature, and by browsing the Medline Thesaurus (MeSH).

10.2.2.3 Management of references

As several databases were searched, some degree of duplication resulted. In order to manage this issue, the titles and abstracts of bibliographic records were downloaded and imported into EndNote bibliographic management software to remove duplicate records.

The final EndNote Library file consisted of 1,544 records. A further 120 studies were identified by hand searching or from the survey respondents.

10.2.3 Further searches

Additional searching was undertaken on the Internet. Specific sites were searched, including the Department of Health, National Institute of Clinical Excellence (NICE), Medicines and Healthcare products Regulatory Agency (MHRA), and the US Food and Drug Administration, Center for Drug Evaluation and Research (FDA CDER). Ongoing trials registers were searched: Clinical Trials Gov and Current Controlled Trials. A search of the Internet using a Meta-Search engine (Copernic) and general search engine (Google) was also undertaken. Nothing of particular relevance was found, other than a Health Service Circular about a UK MS drug risk-sharing scheme, with most results looking at the post market surveillance of safety, efficacy and adverse events of drugs.

10.2.4 Search Strategies

10.2.4.1 MEDLINE strategy (Ovid Gateway). Internet. 1996-2003/November week 2.

The MEDLINE database was searched on the 26th November 2003. 989 records were retrieved. A fairly precise economic filter with additional terms for reimbursement and modelling was used in combination with terms for post marketing, drug approval, and risk sharing.

1. economics/
2. exp "costs and cost analysis"/
3. economics, pharmaceutical/
4. exp insurance, health, reimbursement/
5. cost effect$.ti,ab.
6. cost benefit$.ti,ab.
7. cost util$.ti,ab.
8. economic evaluation$.ti,ab.
9. technology assessment$.ti,ab.
10. pharmacoeconomic$.ti,ab.
11. exp models, economic/

12. exp decision support techniques/
13. markov.ti,ab.
14. decision analysis.ti,ab.
15. reimbursement.ti,ab.
16. or/1-15
17. Clinical Trials, Phase IV/
18. clinical trial phase iv.pt.
19. (phase IV or Phase IIIB or Phase V).ti,ab.
20. exp Product Surveillance, Postmarketing/
21. (post market$ or postmarket$ or post-launch$ or postlaunch$).ti,ab.
22. (product launch or productlaunch).ti,ab.
23. (post approval or postapproval).ti,ab.
24. (post licens$ or post licenc$).ti,ab.
25. post authori?ation.ti,ab.
26. confirmatory stud$.ti,ab.
27. exp Drug Approval/
28. (drug$ adj2 (approval or approved)).ti,ab.
29. (pharmaceut$ adj2 (approval or approved)).ti,ab.
30. (medicin$ adj2 (approval or approved)).ti,ab.
31. fast track$.ti,ab.
32. ((interim or conditional or full or final) adj2 approval).ti,ab.
33. (market$ adj2 (approval or approved)).ti,ab.
34. (accelerat$ adj2 (approval or approved)).ti,ab.
35. (4th hurdle or fourth hurdle).ti,ab.
36. (two stage adj2 (approval or appraisal)).ti,ab.
37. Risk Sharing, Financial/
38. risk shar$.ti,ab.
39. or/17-38
40. 16 and 39
41. Animal/
42. Human/
43. 41 not (41 and 42)
44. 40 not 43

10.2.4.2 EMBASE Strategy (Ovid Gateway), Internet. 1996-2003/week 47. 26th November 2003

The EMBASE database was searched on the 26th November 2003. 877 records were retrieved using a translation of the search strategy used in MEDLINE.

1. economic evaluation/
2. cost effectiveness analysis/
3. cost benefit analysis/
4. cost minimization analysis/
5. cost utility analysis/
6. cost effect$.ti,ab.
7. cost benefit$.ti,ab.
8. cost util$.ti,ab.
9. economic evaluation$.ti,ab.
10. technology assessment$.ti,ab.
11. pharmacoeconomic$.ti,ab.
12. Statistical Model/
13. decision theory/
14. markov.ti,ab.
15. decision analysis.ti,ab.
16. reimbursement/
17. pharmacoeconomics/
18. or/1-17
19. postmarketing surveillance/
20. phase 4 clinical trial/
21. (post market$ or postmarket$ or post-launch$ or postlaunch$).ti,ab.
22. (phase IV or Phase IIIB or Phase V).ti,ab.
23. (product launch or productlaunch).ti,ab.
24. (post approval or postapproval).ti,ab.
25. (post licens$ or post licenc$).ti,ab.
26. post authori?ation.ti,ab.
27. confirmatory stud$.ti,ab.
28. drug approval/
29. (drug$ adj2 (approval or approved)).ti,ab.
30. (pharmaceut$ adj2 (approval or approved)).ti,ab.

31. (medicin$ adj2 (approval or approved)).ti,ab.
32. fast track$.ti,ab.
33. ((interim or conditional or full or final) adj2 approval).ti,ab.
34. (market$ adj2 (approval or approved)).ti,ab.
35. (accelerat$ adj2 (approval or approved)).ti,ab.
36. (4th hurdle or fourth hurdle).ti,ab.
37. (two stage adj2 (approval or appraisal)).ti,ab.
38. risk management/
39. risk shar$.ti,ab.
40. or/19-39
41. 18 and 40
42. exp animal/ or exp animal experiment/
43. exp nonhuman/
44. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dogs or dog or cats or bovine or sheep).ti,ab,sh.
45. exp human/ or exp human experiment/
46. 42 or 43 or 44
47. 46 not (46 and 45)
48. 41 not 47

10.2.4.3 CINAHL Strategy (Ovid Gateway), Internet. 1996-2003/November week 2. 27th November 2003

The CINAHL database was searched on the 27th November 2003. 91 records were retrieved using a strategy similar to that used in MEDLINE.

1. exp Economics/
2. exp "financial management"/
3. exp "financial support"/
4. exp "financing organized"/
5. exp "business"/
6. 2 or 3 or 4 or 5
7. 1 not 6
8. health resource allocation.sh.
9. health resource utilization.sh.
10. 8 or 9

11. 7 or 10
12. cost effect$.ti,ab.
13. cost benefit$.ti,ab.
14. cost util$.ti,ab.
15. economic evaluation$.ti,ab.
16. pharmacoeconomic$.ti,ab.
17. technology assessment$.ti,ab.
18. INSURANCE, HEALTH, REIMBURSEMENT/
19. reimbursement.ti,ab.
20. Models, Statistical/
21. markov.ti,ab.
22. decision analysis.ti,ab.
23. or/12-22
24. 11 or 23
25. Product Surveillance/
26. (phase IV or Phase IIIB or Phase V).ti,ab.
27. (post market$ or postmarket$ or post-launch$ or postlaunch$).ti,ab.
28. (product launch or productlaunch).ti,ab.
29. (post approval or postapproval).ti,ab.
30. (post licens$ or post licenc$).ti,ab.
31. post authori?ation.ti,ab.
32. confirmatory stud$.ti,ab.
33. Drug Approval/
34. (drug$ adj2 (approval or approved)).ti,ab.
35. (pharmaceut$ adj2 (approval or approved)).ti,ab.
36. (medicin$ adj2 (approval or approved)).ti,ab.
37. fast track$.ti,ab.
38. ((interim or conditional or full or final) adj2 approval).ti,ab.
39. (market$ adj2 (approval or approved)).ti,ab.
40. (accelerat$ adj2 (approval or approved)).ti,ab.
41. (4th hurdle or fourth hurdle).ti,ab.
42. (two stage adj2 (approval or appraisal)).ti,ab.
43. risk shar$.ti,ab.
44. or/25-43
45. 24 and 44

10.2.4.4 Health Management Information Consortium (HMIC) Strategy, Ovid Webspirs. 1996-2003/11. 27th November 2003

The HMIC databases were searched on the 27th November 2003. 57 records were found.

1. economics/
2. cost effectiveness/
3. economic analysis/
4. economic models/
5. reimbursement/
6. cost effect* in ti,ab
7. cost benefit* in ti,ab
8. cost util* in ti,ab
9. economic evaluation* in ti,ab
10. pharmacoeconomic* in ti,ab
11. technology assessment* in ti,ab
12. decision analysis/ or decision models/
13. markov in ti,ab
14. decision analysis in ti,ab
15. reimbursement in ti,ab
16. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
17. (phase IV or Phase IIIB or Phase V) in ti,ab
18. (post market* or postmarket* or post-launch* or postlaunch*) in ti,ab
19. (product launch or productlaunch) in ti,ab
20. (post approval or postapproval) in ti,ab
21. (post licens* or post licenc*) in ti,ab
22. post authori?ation in ti,ab
23. confirmatory stud* in ti,ab
24. product licensing/ or drug control/ or drug regulations/
25. (drug* near2 (approval or approved)) in ti,ab
26. (pharmaceut* near2 (approval or approved)) in ti,ab
27. (medicin* near2 (approval or approved)) in ti,ab
28. fast track* in ti,ab

29. ((interim or conditional or full or final) near2 approval) in ti,ab
30. (market* near2 (approval or approved)) in ti,ab
31. (accelerat* near2 (approval or approved)) in ti,ab
32. (4th hurdle or fourth hurdle) in ti,ab
33. (two stage near2 (approval or appraisal)) in ti,ab
34. risk shar* in ti,ab
35. #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34
36. #16 and #35

10.2.4.5 NHS Economic Evaluation Database (NHS ECO) Strategy Internal CRO CAIRS interface. 1996-2003/10. 27th November 2003

The NHS EED database was searched on the 27th November 2003. 170 records were retrieved.

s phase(w) IV or Phase(w) IIIB or Phase(w)V
s post(w)market$ or postmarket$ or post(w)launch$ or postlaunch$
s product(w)launch or productlaunch
s post(w)approval or postapproval
s post(w)licens$ or post(w)licenc$
s post(w)authori$
s confirmatory(w)stud$
s drug$(w2)(approval or approved)
s pharmaceut$(w2)(approval or approved)
s medicin$(w2)(approval or approved)
s fast(w)track$
s (interim or conditional or full or final)(w2) approval
s market$(w2)(approval or approved)
s accelerat$(w2)(approval or approved)
s 4th(w)hurdle or fourth(w)hurdle
s (two(w)stage)(w2)(approval or appraisal)
s risk(w)shar$
s s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14 or s15 or s 16 or s17

10.2.4.6 Health Economic Evaluation Database (HEED) strategy. CD-ROM. 1996-2003/11. 27th November 2003.

The HEED database was searched on the 27th November 2003. 58 records were retrieved.

AX=(phase IV) or (Phase IIIB) or (Phase V)
AX=(post market) or (post marketing) or (postmarket) or (postmarketing) or (post-launch) or (post-market) or (post-marketing)
AX=(product launch) or (productlaunch) or (product-launch)
AX=(post approval) or (postapproval) or (post-approval)
AX=(post license) or (post licensing) or (post licensed) or (post licence) or (post licenced)
AX=(post authorization) or (post authorisation)
AX=(confirmatory study) or (confirmatory studies)
AX=(drug approval) or (drug approved)
AX=(pharmaceutical approval) or (pharmaceutical approved)
AX=(medicine approval) or (medicine approved)
AX=(fast track) or (fast tracked) or (fast-track) or (fast-tracked)
AX=(interim approval) or (conditional approval) or (full approval) or (final approval)
AX=(market approval) or (market approved)
AX=accelerated approval
AX=(4th hurdle) or (fourth hurdle)
AX=(two stage approval) or (two stage appraisal)
AX=risk sharing
CS=1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

10.2.5 Internet sites searched

The Internet searches were completed on the 15th and 16th December 2003, using a number of different combinations of search terms for cost/economic and post marketing, risk sharing, phase IV trials, etc.

10.2.5.1 Department of Health

(COIN and POINT databases)
http://www.doh.gov.uk/index.htm

10.2.5.2 National Institute of Clinical Excellence (NICE)

http://www.nice.org.uk/

10.2.5.3 Medicines and Healthcare products Regulatory Agency (MHRA)

http://www.mhra.gov.uk/

10.2.5.4 US Food and Drug Administration Center for Drug Evaluation and Research (FDA CDER)

http://www.fda.gov/cder/

10.2.5.5 Clinical Trials Gov

http://clinicaltrials.gov/ct

10.2.5.6 Current Controlled Trials

http://www.controlled-trials.com/

10.2.5.7 Copernic

http://www.copernic.com/en/index.html

10.2.5.8 Google

http://www.goggle.com/

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