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Bringing medicines to *life*

Securing a future
for innovative medicines:
a discussion paper

Contents

The ABPI is grateful to Jorge Mestre-Ferrandiz, Adrian Towse, Michele Pistollato and Fraser Lewis from the Office of Health Economics for their contribution to this work and for developing the report.

Executive summary

Context
Good research and patient access to new medicines depend on each other (in the UK and globally). Links between the routine use of medicines in the NHS and the ability of the UK to compete for medical research are growing. This is because global pharmaceutical research and development (R&D) is changing. Companies are refocusing their pipelines towards specialised and stratified medicines in order to meet the unmet needs of patients. Healthcare systems are increasingly demanding 'real world' evidence about the value of medicines. NHS patients need to be able to benefit from the best medicines if the UK is to be a global centre for this expanding area of clinical research.

This report:

1. Provides an overview on the changes to drug development, which requires greater links between routine NHS clinical practice and the pharmaceutical R&D environment
2. Explores how the UK could adapt to this new environment to ensure it remains at the forefront in attracting R&D investment
3. Includes case studies to illustrate changes that are already occurring in the UK and at the European level

It is structured around **five global challenges**:

1. The increasing importance of specialised and stratified medicines
2. Rising drug development costs
3. Closer benefit/risk monitoring by regulators over a medicine's lifecycle
4. Increasing demand for 'real world' evidence by Health Technology Assessment (HTA) bodies acting on behalf of payers and regulators, resulting from a growing interest in relative effectiveness
5. The potential disconnect between the evidence needs of regulators and payers/HTA bodies

Key Challenges

Challenge 1: Increasing importance of specialised and stratified medicines
The importance of specialised medicines and stratified (also referred to as personalised) medicine has increased dramatically in the last decade, a trend that will continue. A challenge for personalised medicine lies in current regulatory and HTA structures, which need to adapt to this change. There are currently over 5,600 active products in the global industry research pipeline of which 60% are speciality medicines.

What the UK should do: Ensure Health Technology Assessment (HTA) approaches can better handle specialised and personalised medicine

- The UK has made good progress in stratified medicine with the assessment processes set up byThe National Institute for Health and Care Excellence (NICE) for diagnostics. However, using the incremental cost effectiveness ratio (ICER) threshold approach in technology appraisals, many oncology drugs are not being recommended by NICE, even with the application of the supplementary "end-of-life" criteria introduced by NICE in 2009. The Cancer Drugs Fund (CDF), introduced in England in 2010 and now extended until 2016, has helped many NHS patients gain access to new cancer medicines not appraised or recommended by NICE.
- A recent review of Scottish Medicines Consortium (SMC) processes for rare diseases and end of life care has recommended more flexible approaches for their assessment in the future
- HTA systems should treat oncology and non-oncology treatments differently. Some exemptions already exist for small population orphan and ultra-orphan drugs.
- NICE's Highly Specialised Technology (HST) programme has the potential to make a big difference as to how specialist medicines for very rare diseases are evaluated.

Challenge 2: Rising drug development costs

The costs of researching and developing new medicines have increased over the last four decades. The key driver over the last decade has been the cost of clinical trials. Patient recruitment and retention for clinical trials are one part of this and represent one of the greatest challenges to successful study completion. By attracting clinical research, NHS patients will get the benefits of earlier opportunities to access new treatments.

What the UK should do (1): Improve trial performance by enabling faster patient enrolment:

- The NHS should continuously seek to improve the enrolment process, accelerating the recruitment of patients to clinical trials by time and target. To achieve this, examples include professionalising research services, increased by use of electronic health records, further simplifying processes and eliminating unnecessary administrative procedures, national restructuring to streamline the research governance process and thus the approval of research studies, adopting common templates across the different centres for clinical trials, and using national costing templates and fees.

What the UK should do (2): Mechanism for early access (pre-licensing):

- The UK Early Access to Medicines Scheme (EAMS) can potentially reduce R&D costs and delays in access to medicines. The scheme is, however, currently unfunded. There should be a robust review of the functioning of the scheme in 12 months following its launch in April 2014 to ensure that it is functioning optimally and to consider whether funding would be appropriate.

What the UK should do (3): Strong UK engagement on adaptive licensing

- The UK should engage strongly in the ongoing European discussion on adaptive licensing and leverage its strong track record in clinical research, medicine development and use of electronic health records, to ensure it is a destination of choice for medicines being developed via this pathway.

Challenge 3: Closer benefit/risk monitoring by regulators over a medicine's lifecycle

It has become increasingly important to ensure that drugs continue to be safe and effective (i.e. have a positive benefit/risk profile) post-launch. The European Medicines Agency's (EMA) Roadmap vision and the most recent pharmacovigilance legislation allows Europe's regulatory agency to assess how a new medicine performs in clinical practice. It is important that the NHS becomes a centre for conducting these studies which will help patients in the UK and the rest of Europe.

What the UK should do: Invest in e-health:

- The NHS should implement and improve the adoption of electronic health records. This will enable prospective observational studies and pragmatic clinical trials to track salient research data from patients.
- A number of initiatives around databases are already underway in the UK. The datasets are anonymised without release of personal identifiers. But some challenges remain:
    - Most only cover the management of patients in a primary care setting. Patients prescribed medicines in secondary care will not be coded in such databases. The challenge is joining all the different systems together.
    - Other countries have more comprehensive and complete anonymised medical data available for healthcare research.
- Enhancing the coverage of available data to include more patients, as well as the care provided by specialist physicians, in hospitals, and/or other settings outside of GP practices, would strengthen the UK's ability to conduct studies of patient care and associated safety and effectiveness across a broader range of diseases.

Challenge 4: Increase in demand for 'real world' evidence of relative effectiveness by HTA, payers and regulators

The EMA, the European Network for Health Technology Assessment (EUnetHTA) and others have promoted discussion of both (a) the potential for relative effectiveness of pharmaceuticals to better inform both HTA and post-launch benefit/risk assessment, and (b) practical ways in which evidence of relative effectiveness can be generated and assessed. The focus is on "relative" or "comparative" benefit in routine clinical use.

What the UK should do (1): 'Coverage with evidence development' type arrangements through NICE and the SMC

- NICE and SMC appraisal committees could consider expanding the use of Coverage with Evidence Development (CED) to manage uncertainty, when deciding whether a new product should be made available through the NHS, enabling patients to access a new treatment while relative effectiveness data on value are collected.
- Alternatively, NICE and SMC could support performance linked reimbursement type schemes, with agreements on utilisation and on the cost effectiveness of a new medicine the NHS was able to afford in the 'real world'.
- 'Commissioning through Evaluation', launched by NHS England in 2013, could potentially increase access to treatments when the current evidence base does not demonstrate sufficient clinical and cost effectiveness for its routine use, since they could be funded whilst new evidence is gathered.

What the UK should do (2): Ability to extrapolate NHS data to other countries:

- The NHS should consider how to generate further 'real world' data that can be extrapolated to other countries, making the UK one of the leading countries in the generation of post-launch data. This would increase the likelihood that the UK will remain one of the first countries in which new products are launched.

What the UK should do (3): UK using latest products (standard of care in other countries)

- Using the latest medicines as standard of care ensures, that not only are patients given access to the most innovative technologies, but also that these medicines can be used as the benchmark for future cost-effectiveness evaluations.

What the UK should do (4): Ability to do pragmatic trials pre-launch and post-launch

- As pragmatic trials, both pre and post-launch, become more important, it is essential that the UK provides the right infrastructure to conduct them. This requires the appropriate IT infrastructure, skills and regulation and governance.
- The NHS should work with the industry to facilitate more pre-launch pragmatic trials to make relative effectiveness data available at or shortly after the launch of a new medicine. This would allow HTA bodies to better understand the value of the new medicine.
- The REACT pilot studies are a good example of what can be done post-launch, in real life settings.

Challenge 5: Disconnect between regulators and payers/HTA bodies evidence needs

There is a disconnect between what regulators and HTA bodies expect to see in terms of evidence to meet their information needs. There are also differences in evidentiary needs across different HTA bodies in Europe. This adds to the complexity of clinical trials, an important driver of rising R&D costs over the last decade.

What the UK should do: UK relevant bodies to be a leading force in shaping the EU environment

- NICE is involved in the initiatives at European level which focus on HTA; for example, in the IMI "Get Real" consortium. The NHS should act upon the recommendations of this project. To attract clinical trials to the UK that require a 'real world' setting, the NHS would need to ensure that it is generating and efficiently recording 'real life' clinical data about the effect of treatments on patients. This requires trained and skilled staff and the adoption of new technologies/processes. If the UK does not act, other countries will.
- Both the Medicines and Healthcare products Regulatory Agency (MHRA) and HTA bodies across the UK need to proactively engage with European activities to develop workable early access schemes and innovative pathways such as adaptive licensing, as well as continuing to participate in programmes to offer parallel scientific advice to companies as they plan their clinical trials.

The NHS should consider how to generate further 'real world' data that can be extrapolated to other countries, making the UK one of the leading countries in the generation of post-launch data.

Context

Good research and patient access to new medicines depend on each other (in the UK and globally). Links between the routine use of medicines in the NHS and the ability of the UK to compete for medical research are growing. This is because global pharmaceutical R&D is changing.

Companies are refocusing their pipelines towards specialised and stratified medicine in order to meet the unmet needs of patients. Healthcare systems are increasingly demanding 'real world' evidence about the value of medicines. NHS patients need to be able to benefit from the best medicines if the UK is to be a global centre for this expanding area of clinical research.

Changing requirements for evidence reflect growing recognition of the need to understand how efficacy demonstrated in a Randomised Controlled Trial (RCT) will translate into added benefit in routine clinical use in different healthcare settings, through the use of Pragmatic Clinical Trials (PCTs) or observational studies. Relative effectiveness evidence is also important when assessing whether results in one jurisdiction can be applied elsewhere. Regulators want to use it in post-launch benefit/risk assessments (Eichler et al., 2008). But 'real world' evidence adds more complexity to the way medicines are researched, developed and ultimately used by patients so we need to look at how to reduce the resulting pressures on cost and time, for example, by following patients in research studies using large datasets, including Electronic Health Records (EHRs).

Pharmaceutical companies have been adapting to this new landscape, but uncertainty about its future tends to dampen innovation by increasing regulatory and reimbursement uncertainty, as well as the economic risk associated with drug development. A number of challenges need to be resolved. For example, at what point should companies plan to incorporate more pragmatic approaches to the design of clinical trials, such as the inclusion of active comparators, recruitment of broader populations and conducting studies in usual care settings? How much of this can be done pre-launch? Would greater post-launch emphasis on observational study designs using data from patient registries, data from EHRs and from administrative databases be well received by decision makers? Given the global nature of drug development, how can the industry best adapt to national or regional requirements for additional evidence of relative effectiveness? What is clear is that global drug development is changing, and there are growing links between research and commercial.

A key element to meet these challenges is to understand how changes in drug development will alter the relationship between the research and commercial (supply of medicines for day to day NHS care) elements of the pharmaceutical industry for the NHS.

For each of the identified five global challenges, potential ways forward to address these are set out, focusing on what the UK should do to ensure it can be a leading location for biomedical R&D, both pre and post-launch. Several solutions and UK actions have been identified – which should be seen as complementary. Moreover, some of the solutions can help address more than one challenge. We now take each of these challenges in turn.

Challenge 1:

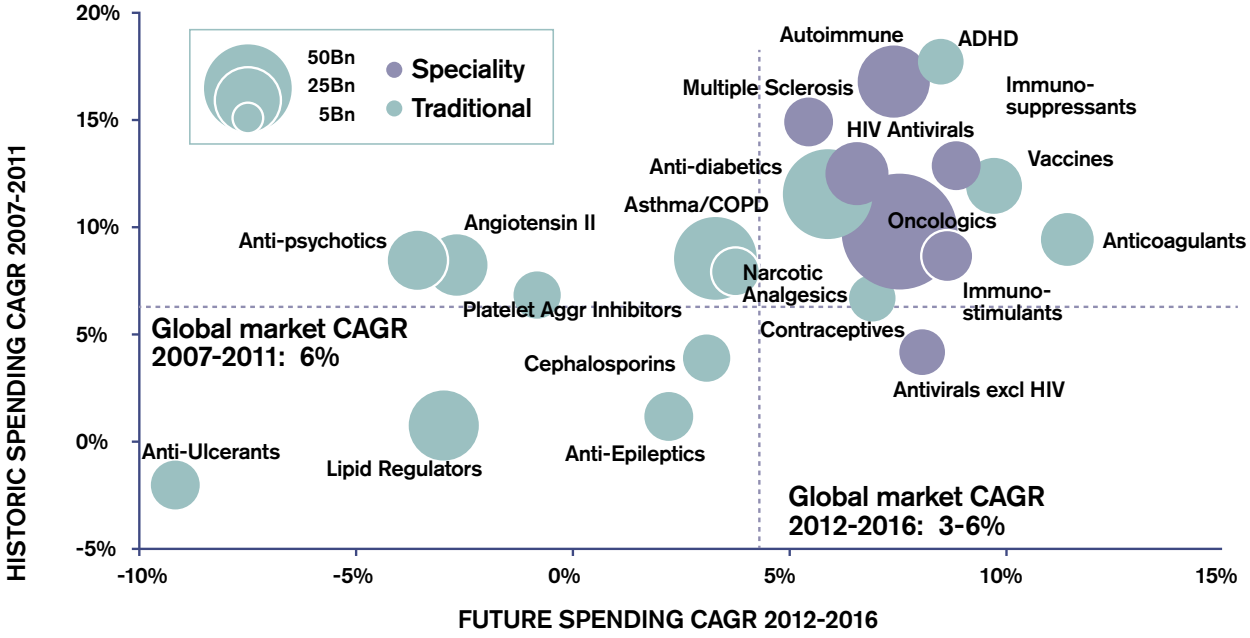
Increasing importance of specialised and stratified medicines

The importance of specialised medicines and stratified medicine has increased dramatically in the last decade, a trend that will continue. Patient stratification has attracted much attention due to the expectation that it will enhance value by allowing a selection of sub-groups of patients to increase treatment efficacy or reduce patient exposure to potential side effects/ toxicity when accompanied by diagnostic testing.

In 2003, specialty medicines represented 15% of global pharmaceutical sales; by 2013, this percentage had increased to 24% (IMS, 2013). Figure 1 shows spending and growth in leading therapy areas, globally. All of the 'specialty' therapy areas are in the upper right quadrant – implying highest growth rates in the past and in the future; plus some are also depicted by the biggest 'bubbles', representing highest spend.

The current pipeline sees a high proportion of specialist driven products and biologics. There are currently over 5,600 active products in the global industry research pipeline. 60% of those are specialty medicines. Moreover, approximately 33% of all products in the pipeline at all stages are biologics (IMS, 2013). The pharmaceutical industry has shifted its R&D focus from its historical concentration on small molecule drugs to include a rapidly increasing number of biotechnology products (Tufts, 2013a).

Figure 1: Future growth by therapy area driven



Source: IMS Institute for Healthcare Informatics, 2012

As of December 2013, the current pipeline sees a high proportion of specialist driven products and biologics. There are currently over 5,600 active products in the global industry research pipeline. 60% of those are specialty medicines. Moreover, approximately 33% of all products in the pipeline at all stages are biologics.

IMS, 2013

In Europe, 39 medicines approved by the EMA contain pharmacogenetic information in the summary of product characteristics. Oncology has attracted most attention from the U.S. Food and Drug Administration (FDA) in terms of including information about pharmacogenomics biomarkers in drug labels. The Office of Health Economics (OHE) analysis indicates that over 30% of drugs with pharmacogenomic biomarkers in drug labels listed in the FDA's website refer to oncology drugs (39 oncology drug labels), followed by psychiatry with 27 drug labels. Analysis based on pipeline information (found in IMS Lifecycle database) shows that nearly 40% of products in development associated to a biomarker are for oncology, followed by nearly 20% for the central nervous system.

A challenge for personalised medicine in many countries lies in current reimbursement arrangements. Garau et al. (2013) argue that current pricing and reimbursement systems for diagnostics in many countries are not efficient, because prices for diagnostics are often driven by administrative practices and expected production costs rather than their value to the healthcare system.

Solution: Set up correct incentives for development and availability of medicines and diagnostics

Garau et al. (2013) offer a potential solution to the value assessment process to molecular diagnostics, by suggesting a two-part approach. Companion diagnostics introduced at the launch of the medicine should be assessed through drug assessment processes considering a broad range of value elements and a balanced analysis of diagnostic impacts. A separate diagnostic-dedicated committee using value based pricing principles should review other diagnostics lying outside the companion diagnostics-and-drug 'at-launch' situation. Aspects of value in a pharmacogenetic test, such as its ability to reduce time delays in selecting the right treatment, would need to be captured in any comprehensive assessment of the value of a companion diagnostic. Towse and Garrison (2013) suggest offering appropriate economic incentives to encourage more rapid progress in the development and availability of medicines and diagnostics. This would require adjustments to existing pricing, evidence and intellectual property approaches.

Towse and Garrison (2013) also argue for flexible (including indication-specific) pricing for new medicine as well as their companion diagnostics. This implies, according to these authors, a greater willingness on the part of payers to accept prices that reflect value (for both medicines and diagnostics) and thus allowing price flexibility for medicines as evidence of their value for different groups of patients emerges over time. These are similar to the recommendations of the Academy of Medical Sciences (Academy of Medical Sciences, 2013).

What the UK should do: Ensure HTA approaches can better handle specialised and personalised medicine

The UK has made good progress in stratified medicine with the assessment processes set up by NICE for diagnostics. However, using the current Incremental Cost Effectiveness Ratio (ICER) threshold approach in technology appraisals, many oncology medicines are not being recommended by NICE, even with the application of the supplementary 'end-of-life' criteria introduced in 2009. The CDF, introduced in England in 2010 now extended until 2016 (NICE, 2013a), has helped many NHS patients gain access to new medicines. It is used to fund drug treatments, including radiopharmaceuticals, for patients who have been unable to access a medicine recommended by their oncologist. This includes medicines that are either not routinely available on the NHS or have not been approved or appraised by NICE. It also provides fast track access to cancer medicines that are awaiting NICE guidance as well as access to medicines for less common cancers. O'Neill (unpublished) shows trends in NICE decisions for oncology drugs pre and post-CDF. Figure 2 shows this analysis.

Figure 2: Trends in NICE decisions for oncology drugs pre and post-CDF (Q4 2010 to Q1 2013)

Source: O'Neill (unpublished)

Figure 2 shows how the proportion of 'not recommended' decisions for oncology medicines has more than doubled since the introduction of the CDF (58% post-CDF vs. 24% pre-CDF), while the proportion of 'restricted' decisions has fallen significantly, from 41% to 9%. The proportion of positive recommendations has fallen only slightly, from 26% to 24%.

The setting up of the CDF was an acknowledgment that existing HTA approaches in England are inappropriate for the assessment and appraisal of the value of oncology treatments.

A recent review of SMC processes (Scottish Government, 2014; SMC, 2013) for rare diseases and end-of-life care has recommended more flexible approaches for their assessment in the future. The SMC is working with stakeholders to introduce these new approaches as quickly as possible.

HTA systems based on both clinical and cost effectiveness could treat oncology and non-oncology treatments differently in their assessments, in the same way that we have observed for orphan and ultra-orphan medicines. At least two exemptions are possible. First, exemption from submitting a full cost effectiveness dossier at launch – but with a proviso that further post-launch data is collected. This might be particularly relevant if there are high levels of uncertainty at launch. This option is consistent with other solutions provided below (moving some pre to post-launch work and CED-type approaches). Second, a higher threshold could be used for oncology treatments, reflecting the priority given by the Government to treating cancer.

40% of products in development associated to a biomarker are for oncology... nearly 20% for the central nervous system.

Case study: Single payment access scheme for gefitinib with patient follow-up

A single payment Patient Access Scheme was introduced in September 2009 which formed part of the NICE assessment for gefitinib (manufactured by AstraZeneca) for the first line treatment of locally advanced or metastatic non-small-cell lung cancer, for patients who test positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation.

The single fixed payment under the scheme is triggered at the order of the third 30 day pack and covers a patient for their total supply of gefitinib treatment, regardless of how long that may be. This scheme was based on the mean duration of treatment observed in a Phase III, randomised, open-label trial (8.8 months). AstraZeneca agreed to analyse the duration of therapy in anonymous patient data from those patients receiving gefitinib through the scheme to evaluate whether the NHS receive the expected benefit of the programme. For this purpose, AstraZeneca provides a registry to capture distribution of gefitinib.

A retrospective study (Vioix et al., 2013) was carried out to validate the length of therapy in a cohort of patients with upto three years follow-up. It included those patients registered on the database prior to the end of 2012, fulfilling NICE eligibility criteria and receiving at least three packs for which the NHS was invoiced. The results of this observational study confirm the average length of gefitinib therapy and mean number of packs dispensed in the scheme exceed that assumed by NICE.

This scheme provides three valuable pieces of information from an HTA perspective: i) it provides an assessment of effectiveness as it captures variation in duration of therapy across a live patient population; ii) it provides an accurate estimate of the true cost; iii) it has broad scope in that it can provide estimates of effectiveness and cost both locally (e.g. Trust level) and nationally.

Source: AstraZeneca; NICE, 2010; Vioix et al., 2013

The particular challenges faced with developing medicines for very rare conditions have been recognised by the use of the orphan designation for such treatments. In July 2012, the UK Parliament decided that, as of April 2013, NICE would take over the responsibility of assessing ultra-orphan medicines from the Advisory Group on Nationalised Specialised Service (AGNSS). Under this new remit, NICE has also accepted that a different approach is needed and is developing its HST process.

Following the publication of NICE's *Interim Process and Methods of the Highly Specialised Technologies Programme* (NICE, 2013b), NICE recommendations on the use of highly specialised technologies are made by an independent advisory committee, called the Highly Specialised Technologies Evaluation Committee. The decision making framework to be used by this Committee builds on the work by AGNSS. The HST programme has the potential to make a big difference to how medicines for very rare diseases are evaluated but, as ever, 'the devil will be in the detail'.

When the evidence of clinical effectiveness or impact of a highly specialised technology on other health outcomes is either absent, weak or uncertain, the Evaluation Committee may recommend that the technology is used only in the context of research or the technology is recommended as an option, but also that research is conducted. The latter seems aligned with a CED-type arrangement.

Case study: Cancer Research UK (CRUK)-AstraZeneca-Pfizer: Stratified Medicines

Cancer Research UK (CRUK) working together with AstraZeneca and Pfizer. The future potential of personalised healthcare for cancer lies in the ability to match a therapeutic option or medicine to the mechanism underlying or driving a patient's tumour. As an initial, but major, step towards this future, CRUK aims to establish a national capability making standardised, high quality, cost effective genetic testing of tumours available for people with cancer. So, as and when targeted treatments become available, doctors will have access to the tests needed to help them decide the most suitable drugs for each individual patient. The initiative is focused initially in lung cancer only, and will develop an associated bespoke screening capability. However, the programme could pave the way for development of a broader screening capability and other tumour types in the future.

As part of this collaboration, AstraZeneca and Pfizer have made available up to 14 oncology drugs (up to 12 from AstraZeneca, and 2 from Pfizer) to CRUK's 'central pharmacy'. Once doctors know the characteristics of the patient (based on the genetic testing above), the patient will have access to the appropriate drug. Some of these medicines have already been approved by the European regulator, EMA, and some are still in development.

In addition, AstraZeneca is collaborating with CRUK's "Experimental Cancer Medicine Centre (ECMC) Network" (which comprises some 18 cancer centres across the UK) to drive faster patient enrolment in clinical trials for lung cancer. This has been achieved by agreeing a unique study protocol (with Birmingham's CRUK Clinical Trials Unit), which will then enable all other centres willing to participate in a clinical trial to enrol directly without further delay.

In the future, the way cancer patients are treated will change. Cancer will no longer be diagnosed by 'type', but by patient's molecular characteristics. For companies to undertake trials in the UK, patients need to be stratified in a timely manner and then be provided the most suitable treatment. If there is no infrastructure to do that, companies will go elsewhere.

Source: AstraZeneca

Challenge 2:

Rising drug development costs

R&D costs of successful new medicines (including drugs that fail to reach the market) have increased over the last four decades. They have risen from $199 million per new medicine in the 1970s to $1.9 billion in the 2000s (Mestre-Ferrandiz et al., 2012). Four factors drive this increase: out-of-pocket costs; success rates; development times; and cost of capital.

The key driver over the last decade has been out of pocket costs and, in particular, the cost of clinical trials. The cost of clinical trials is affected by the cost per patient and the number of patients required to collect sufficient data. The complexity of clinical trials has increased over time – another important driver of increasing cost. Some inefficiencies have been identified in clinical trials. This includes each clinical trial to test a new medicine candidate is being typically organised *de novo*, requiring substantial effort, cost and time, and delays in the writing and approval of protocols for clinical trials, as usually protocols need to be submitted to many institutions (US President's Council of Advisors on Science and Technology, 2012). Barker (2010) supports this view and raises lack of flexibility in trial design and analytical methods as a key problem.

Solution 1: Faster patient enrolment in clinical trials

Patient recruitment and retention for clinical trials is recognised as one of the greatest challenges to successful study completion, and are a major cause of drug development delays (Tufts, 2013b). Around 80% of clinical trials do not meet patient recruitment timelines, and on average last 30-42% longer than companies initially plan for (Quintiles, undated; Shah, 2013). The longest delays come from Phase III studies, which last on average 6.2 months longer than anticipated (Hess and Litalien, 2005). The average number of patients included in clinical trials has doubled in recent years which exacerbate patient recruitment problems.

More complex clinical trial protocols are demanding more investigative site personnel and study volunteers, leading to longer clinical trials and increasing difficulty in recruiting and retaining patients (Tufts CSDD, 2008).

Thus, ensuring faster patient recruitment would reduce time and costs of clinical trials. One way of achieving faster patient recruitment would be streamlining governance to ensure bottlenecks in running clinical trials are minimised.

Case study: The APIPPRA study

The APIPPRA (Arthritis Prevention In the Pre-clinical Phase of RA with Abatacept) study will enrol patients over a 24 month period, targeting over 200 individuals at high risk of developing rheumatoid arthritis. It is anticipated patient recruitment will begin in quarter 2 of 2014. The study is led by Professor Andrew Cope from the Guy's and St Thomas' Biomedical Research Centre at King's College London and is supported by the National Institute for Health Research (NIHR). The objective is to test the use of Abatacept, a Bristol-Myers Squibb drug already marketed for the treatment of moderate to severe RA, and its potential application in arthritis prevention.

The support of the NIHR Translational Research Partnership (TRP) allows for the inclusion of 31 of the UK's leading academic and NHS research centres as well as trial centres in the Netherlands. The scale of the trial underscores the ability of the NHS and its partners to cooperate at scale to tackle the nation's most pressing healthcare issues. Since its establishment in April 2006, the NIHR has worked with key partners to transform research in the NHS.

Source: Bristol-Myers Squibb

Case study: Accelerating clinical trial set-up

Bristol-Myers Squibb has worked to improve communications with academic institutions with the aim of making future partnerships more productive and, in particular, streamlining the recruitment process for clinical trials. Recent studies at the Royal Marsden have been characterised by rapid start up and recruitment, with the highest number of patients recruited for a BMS-sponsored study at any one site globally.

Across the NHS, the main challenge for the future is to replicate successes in first-patient recruitment as well as extending it to faster recruitment of subsequent trial patients. One contributing factor could be the wider use of mandatory nationally-standardised fee structures and template contracts, which would help reduce bureaucracy and set-up times.

Source: Bristol-Myers Squibb

Solution 2: Use of adaptive design in clinical trials

There is great interest in the possibility that clinical trials can be designed with adaptive features (FDA, 2010). Such a design has the potential to speed up the process of drug development or can be used to allocate resources more efficiently without lowering scientific and regulatory standards. This is especially welcome if at the same time the basis for regulatory decision making is improved (EMA, 2007).

Simple adaptive trial designs – such as early study terminations due to futility – are becoming widely adopted throughout the industry, most notably in Phase III studies. Although a number of case examples of sophisticated adaptive designs exist, the adoption of these designs – including adaptive dose-finding and seamless Phase II/III studies – has been slow. However, more sophisticated adaptive designs applied to exploratory phase clinical trials hold strong potential to impact success rates in later phase development (Getz et al., 2013). Other benefits of adaptive trial designs include saving financial resources by helping to reduce the number of protocol amendments. While nearly 60% of all protocols used in clinical trials for new medicines are amended during the trial, one-third of those changes could have been avoided - with better initial study design and improved recruitment of study volunteers (Tufts CSDD, 2011). Adaptive trial designs offer cross functional teams within organisations to 'stress-test' the protocol before it is finalised, through scenario planning and trial simulation. The implementation of each amendment costs organisations nearly $500,000 ($US) in direct costs and requires 60 days to implement (Getz et al., 2013).

What the UK should do (1): Improve trial performance by enabling faster patient enrolment

The OLS Blueprint (OLS, 2009) highlighted that the UK was losing ground internationally as a valued country site for undertaking clinical investigations of medical technology and later-phase clinical trials for medicines, and recruitment was mentioned as a reason for that.

In 2010 the Academy of Medical Sciences was invited by the UK Government to review the regulation and governance of health research and make recommendations to improve current processes. The review identified several bottlenecks, including:

- Delays and duplication in obtaining research permission from NHS R&D Trusts;
- Complexity and inconsistent bureaucracy across the regulatory pathway e.g. access to patient data;
- A lack of proportionality in the regulation of clinical trials.

The NHS should continuously seek to improve the enrolment process, accelerating the recruitment of patients to clinical trials to time and target. Ways to do that (some already recommended by the Academy's report (Ford, 2011)) include professionalising research services, increased use of EHRs, further simplifying process and eliminating unnecessary administrative procedures, national restructuring to streamline the research governance process and thus the approval of research studies (by for instance, having a single ethics approval for all NHS Trusts), adopting common templates across the different centres for clinical trials, and national costing templates and fees. EHRs in particular can be leveraged to improve speed and quality of the patient recruitment process. A readily accessible global health data repository in the form of EHR can help to identify relevant patients for clinical trials with diminished chances of screen failures, recruit sites in close proximity to the relevant patient population

to improve recruitment chances, and enhance patient awareness of trials through their care provider (Shah, 2013). Some of our case studies illustrate how patient recruitment can be accelerated using a combination of such initiatives. We acknowledge the progress made in the formation of the Health Research Authority (HRA), with its focus on streamlining research governance.

What the UK should do (2): Mechanism for early access (pre-licensing)

The UK launched its *Strategy for UK Life Sciences* in December 2011. A number of actions have progressed slowly and are yet to deliver their stated ambition. The EAMS promised to facilitate patient access to new medicines, up to a year before marketing authorisation for selected medicines where there is a high unmet need. In March 2014 it was announced that the EAMS would be implemented in April 2014. The programme is aimed at innovative drugs which target life threatening or seriously debilitating conditions for which there are either no treatment options or treatments are not satisfactory.

There will be three stages to this scheme. At Stage 1, the MHRA will issue a 'Promising Innovative Medicine' designation. This will be based on, for example, early clinical data from Phase II studies. Stage 2 entails an 'Early Access to Medicines' scientific opinion, issued by the MHRA. This is designed to support the prescriber to make a decision with a patient on using the medicine when it is still unlicensed or used off-label. At this stage, the MHRA and NICE will also make available joint parallel scientific advice meetings in relation to clinical development programmes. At Stage 3, and once the product is licensed, medicines developed through the EAMS will be appraised by NICE for routine use on the basis of the evidence collected in the earlier stages of the scheme. Medicines in the scheme, once licensed, will be commissioned by NHS England (NHSE) through its specialised commissioning arrangements which deliver a single national approach to commissioning.

The EAMS can potentially reduce R&D costs and delays in access to medicines. The EAMS has been received positively by the industry in the UK – although the scheme is currently unfunded which means companies have to bear the risk associated with the upfront investment that will be required to participate in the scheme. There should be a robust review of the functioning of the scheme in 12 months from its April 2014 launch to ensure it is functioning optimally and to consider whether funding would be appropriate.

The French *"Autorisations Temporaires d'Utilisation"* ("Temporary Authorisations for Use") or ATU procedure is similar to the EAMS. Since its establishment in 1994, the ATU has made it possible to use new medicines to treat several tens of thousands of patients in a situation of treatment failure, several months before these medicines have obtained a marketing authorisation. The aim of ATUs is to provide early access to new promising treatments where a genuine public health need exists, i.e. in the treatment of patients suffering from serious disease and having reached a situation of therapeutic impasse. Since 1994, more than 400 medicinal products have been the subject of applications for an ATU and a benefit/risk ratio assessment. ATUs do not slow down the implementation or continuation of clinical trials intended to provide detailed and essential answers relative to the benefit/risk ratio of a medicinal product.

What the UK should do (3): Strong UK engagement on adaptive licensing

The UK should engage strongly in the ongoing European discussion on adaptive licensing (see Challenge 4) and leverage its strong track record in clinical research, medicine development and use of electronic health records, to ensure it is a destination of choice for medicines being developed via this pathway.

Around 80% of clinical trials do not meet patient recruitment timelines, and on average last 30-42% longer than companies initially plan for.

Challenge 3:

Closer benefit/risk monitoring by regulators over a medicine's life cycle

There is an increased emphasis from regulators on post launch safety, with considerable uncertainty about what the future will bring with continued development of the data infrastructure in both the EU and the US to monitor safety signals post-launch.

In order to meet regulatory requirements it is no longer sufficient to get new medicines to the market (medicines meeting traditional safety and efficacy standards for licensing purposes at the point of launch). It has become increasingly important to ensure that those medicines continue to be safe and effective (i.e. have a positive benefit/risk profile) post-launch. This is reflected in the EMA Roadmap vision of looking at benefit/risk over the lifecycle of a medicine, and by the introduction of the new pharmacovigilance legislation (implemented from July 2012), which enables the EMA to require companies to provide, in certain circumstances, additional Post Authorisation Efficacy Studies (PAES), as well as Post Authorisation Safety Studies (PASS). This allows the regulatory agency to assess how a new medicine performs in clinical practice and facilitates a closer monitoring of the benefit of a medicine, as well as its risks, throughout its lifecycle.

Solution: Improve data (IT) infrastructure

The range of possible applications of Information and Communication Technologies (ICT) in the health sector is enormous. Unfortunately, implementing ICTs in clinical care has proven to be a difficult undertaking (OECD, 2011) for many countries and not just for the NHS. A widely recognised source of inefficiencies in healthcare systems is the fragmentation of the care delivery process and the poor transfer of information (Mestre-Ferrandiz et al., 2012). The efficient sharing of health information is, however, indispensable for the effective delivery of care and the more efficient use of resources. The implementation of privacy and security requirements is proving particularly challenging in the case of EHRs and constitutes a main barrier to system-wide exchange of information in many countries.

Improvements in ICT could lead to a wide range of benefits:

- Better integration of primary and secondary care, allowing monitoring and following patients throughout the entire treatment pathway.
- Possibility of doing observational studies, at a reduced cost, which would allow the generating of relative effectiveness and safety data.

Already in 2005, new EU legislation introduced a requirement for the submission (in the application for authorisation of a medicinal product) of the risk management system, when appropriate, by applicants and/or marketing authorisation holders. This legislation aimed to augment and strengthen spontaneous reporting of adverse drug reactions. Planning of pharmacovigilance would also guide the use of routine electronically collected data within health services to provide rapid investigation of predicted or emerging safety concerns. Risk management is a continuing process throughout the lifecycle of a medicinal product (EMA, updated). EudraVigilance is one of the main pillars of the European Risk Management Strategy, a joint effort between the EMA and National Competent Authorities to strengthen the conduct of pharmacovigilance in the EU. EudraVigilance is a data processing network and management system for reporting and evaluating suspected adverse reactions during the development and following the marketing authorisation of medicinal products in the European Economic Area. The first operating version was launched in December 2001.

There are also ongoing discussions at European level where companies are investigating designing protocols (for example, for PASS) that also collect data for value assessment.

It is essential that the IT infrastructure allows for data to be captured routinely, and that this data is of high quality.

What the UK should do: Invest in e-health

The NHS should implement and improve the adoption of EHRs to track salient research data from patients in prospective observational studies and pragmatic clinical trials. This would allow important questions about the effects of medical interventions to be answered. For instance, large scale datasets better reflect 'real world' use (i.e. effectiveness) of medical interventions rather than tightly controlled experimental use (i.e. efficacy). Moreover, large administrative datasets are frequently used by pharmaceutical researchers to discern rare but dangerous side effects of medications that were approved for sale based on trials of a few thousand people but may eventually be used by millions of people per year. The importance of research with EHR data has also been recognised in the Department of Health's research strategy (Department of Health, 2005). The datasets are anonymised without the release of personal identifiers.

Case study: 'Real world' duration of dual antiplatelet therapy following acute coronary syndrome

By linking a range of different patient level datasets, the 'real world' duration of dual antiplatelet therapy following acute coronary syndrome was estimated for a broad sample of a patients across the UK. This estimate was then used to inform HTA submissions for Brilique (manufactured by AstraZeneca) which resulted in positive NICE and SMC recommendations, and also enabled an assessment of compliance with current clinical guidelines. Using the MINAP (Myocardial Ischaemia National Audit Project) national clinical audit database relevant patients were first identified. Longitudinal records for a subset of this patient group were then created by General Practice Research Database (GPRD) using primary care data linked to hospital episode data (HES). MINAP was commissioned by the Healthcare Quality Improvement Partnership (HQIP) and is maintained by the National Institute for Cardiovascular Outcomes Research at University College London.

Source: AstraZeneca

Case study: Linking datasets for inflammatory bowel disease

Takeda's ongoing research in inflammatory bowel disease (IBD) requires real world studies to inform as to the timing and effectiveness of tumour necrosis factor (TNF) cycling, to evaluate inadequate response to anti-TNF treatment, and to assess the impact of treatment failure or loss of effectiveness on clinical and patient-focused outcomes as well as on subsequent healthcare resource utilization and associated costs.

At present, there is an initiative by the IBD Registry Board to create the UK IBD Registry that will provide the first ever UK-wide repository of anonymised IBD data for prospective audit and research purposes driving continuous improvement in patient care and access to care across the UK. This registry is also aimed at collecting information on outcomes and will potentially include health related quality of life and health care resource utilisation in IBD patients. The set up for the data collection process will take time; and it is expected that it will take years before the UK IBD Registry will be ready for medical research use. The IBD Registry Board is a collaboration between various medical professional associations and is financially supported by industry partners and charitable trusts.

Source: Takeda

A number of initiatives are already underway in the UK. These highlight a number of current problems that need to be addressed to maximise the benefits from these databases. Primary care data contained in the Clinical Practice Research Database (CPRD) and in The Health Improvement Network (THIN) in the UK are an excellent source for pharmacoepidemiological and pharmacoeconomic studies. They provide relatively complete medical histories and hence the use of medicines can be identified. Studies can be undertaken to assess the characteristics of the patients being prescribed medicines of interest and how such medicines may then impact outcomes in terms of safety and effectiveness.

Case study: Datasets at national level

Scotland
Electronic Data Research and Innovation Service (eDRIS). eDRIS* is a new data provision and analytics service offered by the NHS in Scotland which has access to a range of clinically linked national datasets. For example, using an individual patient's Community Health Index number (CHI) (the Scottish equivalent of the NHS number in England and Wales), eDRIS can link together prescriptions dispensed from a community pharmacist, secondary care consultant outpatient appointments, in patient/day case treatment episodes, and vital events such as registrations of births and deaths. Prescribing information in a secondary care setting in not yet available, nor currently is the linkage of patient records which reside within local GP practice systems. Progress on the latter is being made through SPIRE** (Scottish Primary Care Information Resource), a service run by NHS National Services Scotland tasked with extracting records from GP practice systems so as to enable the creation of fully linked primary-through-secondary national datasets. The SPIRE service is scheduled to begin delivery by end 2014/15. Participation in SPIRE is through a voluntary opt-in system at GP practice level. A range of more specialist data sources and registries are available through eDRIS, such as the Hepatitis C Diagnoses Database managed by Health Protection Scotland, and where direct linkage through the CHI is not available matching work can be undertaken.

Industry and third sector organisations are not permitted direct access to the eDRIS safe haven, a secure online data warehouse where datasets may be linked and analyses undertaken using a range of common statistical software packages. Instead, eDRIS analysts can be commissioned to perform requested analyses on linked data, and provide summary results. All such projects must be first approved by the NHS National Services Scotland Privacy Advisory Committee***.

* http://www.isdscotland.org/Products-and-Services/EDRIS/
** http://www.spire.scot.nhs.uk/
*** http://www.nhsnss.org/pages/corporate/privacy_advisory_committee.php

Wales
Secure Anonymised Information Linkage Databank (SAIL). SAIL* is a service operated from the University of Swansea and involves a range of academic and NHS partners in Wales. It provides a range of patient level data sources, across primary and secondary care, with linkage available between these various resources. For example, GP records, hospital episodes, along with births and deaths registrations, plus other more specialist data sets such as the National Cancer Registry for Wales. While a core feature of SAIL is the provision of a safe data haven, where requested linked datasets may be analysed using a range of common statistical software packages. It is also concerned with further developing the methodology and technology required for a privacy protecting remote access system for health-related research and evaluation**. In terms of commercial access the Small Business Research Initiative (SBRI) announced in November 2013 funding to Abertawe Bro Morgannwg University Health Board to allow companies to bid for contracts to find the best way to utilise data from SAIL to improve health services***

* http://www.saildatabank.com
** http://www.saildatabank.com/data-dictionary/publications/87.aspx
*** http://www.ehi2.swansea.ac.uk/en/news.htm?id=110

England
Clinical Practice Research Datalink (CPRD). CPRD* is a service for researchers designed as a one-stop-shop for analytical services involving healthcare data. CPRD, through various NHS partners and also commercial data products (such as IMS Health), has access to a wide range of datasets in England, including linkage of individual patient data. Drawing on the NHS England care.data** initiative, which aims to collect GP held primary care data for all of England and is currently scheduled for late 2014, CPRD may potentially be able to provide clinically linked information across both primary and secondary care on the entire population of England. CPRD has research ethics approval, and it does not release personal or patient level data. Rather, it does the analysis behind a secure firewall and releases aggregated results of that analysis. In addition to providing analytical services on existing routinely collected NHS data to the private sector, CPRD also offer bespoke prospective data capture, aimed at activities such as clinical trials. CPRD is jointly funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA).

* http://www.cprd.com/
** http://www.hscic.gov.uk/article/3525/Caredata

UK
The Health Improvement Network (THIN) database represents a collaboration between two companies, In Practice Systems Ltd (INPS) - who developed Vision software used by general practitioners in the UK to manage patient data, and CSD Medical Research UK (formerly known as EPIC) who then provide access to the data for use in medical research. Users include academic research groups, as well as major pharmaceutical companies. THIN data are collected during routine practice and regularly delivered to THIN. Since THIN data collection began in 2003, over 500 Vision practices have joined the scheme. THIN data currently contains the electronic medical records of 11.1 million patients (3.7 million active patients) equivalent to 75.6 million patient years of data collected from 562 general practices in the UK, covering 6.2% of the UK population. All data are fully anonymised, processed and validated by CSD Medical Research UK. THIN supplies anonymised data (with the identities of patients and practices fully protected) to approved researchers for drug safety and epidemiological studies. Such research will be approved by the appropriate ethics/scientific committee.

http://www.thin-uk.com/

Cancer
National Cancer Intelligence Network, Systemic Anti-Cancer Therapy Dataset (SACT). SACT* is a chemotherapy dataset which, when fully implemented (on 1 April 2014), will be fed by regular submissions from all NHS Trusts in England. This resource comprises of the regimens used to treat cancers, and has the potential to provide very detailed information on both inputs and outcomes, e.g. the regimens used for specific types of cancers and resulting outcomes, along with patient characteristics such as demography. This information could also be linked to other NHS systems (using a patient's NHS number) to provide a comprehensive picture of the overall impact of cancer therapy.

* http://www.chemodataset.nhs.uk

Such databases, however, typically only cover the management of patients in the primary care setting. This has direct implications on any study attempting to identify patients prescribed medicines in secondary care which are not coded in the primary care centre's database. The challenge is joining all the different systems together. Some hospital electronic patient administration systems are excellent and just as good if not better than GP/primary care systems. The problem is that different specialities/departments might have different systems, and that different hospitals have different systems. Thus, it is very hard to join all the systems together. The lack of the link between primary and secondary data has already been highlighted as one of the biggest challenges for the Salford study [see case study]. The only activities really joined together at the moment are simple activity/Hospital Episode Statistics (HES) data.

A potential solution, until full cross-setting data linkage is available for research purposes, is to identify and extract data from the specialist letters that are routinely scanned into GP databases (in the context of privacy arrangements or behind the NHS firewall) which in turn feed into research databases such as CPRD and THIN; the problem is that these methods are expensive and time consuming. For example, just the process of compiling information from retrospective medical chart reviews (which involve compiling information from medical records, (either electronically or in hard copy, in hospitals) can take up to one year.

Other countries have more comprehensive and complete anonymised medical data available for healthcare research than the UK. The limited size of anonymised GP medical record data currently available for research in the UK may significantly limit the ability to undertake research for less common diseases. Countries such as France and Germany, with similar or better anonymised medical record data, have historically limited sharing it with third parties, especially the pharmaceutical industry. However, these countries are now allowing greater access for research purposes.

Enhancing the coverage of available data to include more patients, as well as the care provided by specialist physicians, in hospitals, and/or other settings outside of GP practices would strengthen the UK's ability to conduct meaningful assessment of patient care and associated safety and effectiveness across a broader range of diseases. Initiatives at disease-specific level, such as the Systemic Anti-Cancer Therapy Dataset (SACT) and the IBD Registry, are very welcome. The two Randomised Evaluations of Accepted Choices in Treatment (REACT) pilots recently started are also important and should be closely monitored. These initiatives will, however, take time to develop and roll-out.

Case study: Using GPRD to assess the safe use of a widely prescribed diabetes drug

The following case study gives an example where NHS GP medical records from CPRD were successfully used to assess the safe use of a widely prescribed diabetes medicine. The objective of the study was to assess if GPs were adhering to the regulator-approved product information when prescribing the medicine. The product information warns against prescribing the drug to patients with certain medical conditions (e.g. heart failure), and advises practitioners to monitor response (i.e. change in blood HbA1c levels). Following approval by a national research ethics committee, data were anonymised (all information on patient, doctor and hospital's name address, phone, email, postcode removed), and patient medical and prescription records for approximately 5% of the population were analysed. The analyses show good compliance by GPs in both not prescribing to patients with heart failure, and in monitoring for response. The above study was successful because (1) anonymised patient medical records from GP practices were available; (2) diabetes is a common disease (and many patients were available for analysis); (3) diabetes care is primarily managed by GPs (so relevant practitioners were in the database); and (4) only immediate prescription (and not longer term clinical outcome) was assessed.

Source: Takeda

Other countries have more comprehensive and complete anonymised medical data available for health care research than the UK. The limited size of anonymised GP medical record data currently available for research in the UK may significantly limit the ability to undertake research for less common diseases.

Challenge 4:

Increase in demand for ‘real world’ evidence by HTA, payers and regulators: growing interest in relative effectiveness

The European Commission's High Level Pharmaceutical Forum set out back in 2008 the need for greater use of relative effectiveness evidence in Europe to help identify the value of pharmaceuticals.

Subsequently, the EMA, the European Network for Health Technology Assessment (EUnetHTA) and others have promoted discussion of both (a) the potential for relative effectiveness of pharmaceuticals to better inform both HTA and post-launch benefit/risk assessment and (b) practical ways in which evidence of relative effectiveness can be generated and assessed.

Two elements are of importance when thinking about relative effectiveness (and value). The stress is on 'relative' benefit. It is not enough that the therapy works. The question is "when does it add benefit as compared to existing treatments?" What also matters to patients and payers is that this added benefit can be achieved in routine clinical use of the product as well as in controlled experimental conditions.

Within Europe, national HTA bodies/payers, rather than the EMA, are seen as the drivers of relative effectiveness research at the present time (Towse et al., forthcoming). Requests from HTA bodies include additional post-launch studies collecting 'real world' evidence (in addition to other requests such as modelling based on trial data to predict clinical outcomes in local clinical settings, collecting quality of life data in trials and inclusion of active comparator/s in clinical trials). But, as mentioned in the previous challenge, the implementation of the new pharmacovigilance legislation will give the EMA a more prominent role in commissioning post-launch studies.

Solution 1: Shift from pre to post-launch work, ensuring earlier access to medicines with a commitment to post-launch studies

There is, in principle, a trade-off between investment in pre and post-launch studies. The former increase confidence in likely benefit and benefit/risk at launch but can lead to long delays in patient access to medicines expected to bring benefits. The latter offer more potential for collecting evidence about routine clinical value whilst enabling patients to have access to medicines. Payers and regulators may be willing (through a form of adaptive licensing – see below) to accept a greater degree of uncertainty at launch provided expected benefits and benefit/risk are both of an acceptable size and there is a commitment to post-launch studies.

This issue becomes more important if the industry's model for the EU (and US) will be to seek to launch products earlier and shift data requirements to the post-launch environment. Companies may, of course, try to put more effort in pre-launch to avoid future uncertainty. The EMA is also indicating, as stated above, that it is likely to seek more data post launch to support benefit/risk assessments.

The emergence of an evidence confirmatory path for new medicines is also reflected in the increasing debate and initiatives set up within EMA for the implementation of Adaptive Licensing (AL). The key principle is a trade-off between earlier access for some patients versus an increased level of acceptable uncertainty about benefits and risks, although the degree of uncertainty is expected to diminish with additional evidence generation" (Eichler et al., 2012). The EMA launched in March 2014 an AL pilot project, to explore this approach with real medicines in development by inviting companies to participate in this project (EMA, 2014). A framework to guide the discussions of the individual pilot studies has also been published. These pilots are extremely important to test the feasibility of rolling out AL more generally in Europe. The European Federation of Pharmaceutical Industries and Associations (EFPIA), the European pharmaceutical trade association, is strongly supporting this initiative.

AL differs from the traditional model of licensing where there is a single point in time when a decision on approval is made, and only in limited circumstances further evidence collection and reviews by the regulatory agency are conducted. AL could be seen as an expansion of Conditional Marketing Authorisations (CMAs). CMAs provide early access to a limited number of drugs, while AL would provide earlier access to more drugs in an initial authorisation stage with novel measures to manage risks (Oye et al., 2013). Access to a medicine would be limited to a restricted population, defined on the basis of knowledge about benefits and risks at the time of initial approval. Off-label use would be limited. Oye et al. (2013) argue that with the enactment of the pharmacovigilance legislation in July 2012 (see challenge 3), regulators in Europe have room to pursue AL approaches. Reimbursement for medicines is a member state competency, so it would still be up to individual member states to decide whether or not to reimburse medicines during the initial authorisation phase of AL.

Under AL, particularly in later stages of the medicine lifecycle, evidence generation would not be limited to conventional, randomised controlled trials but would encompass a broader methodology spectrum, including pragmatic clinical trials, clustered randomised controlled trials, observational studies based on electronic medical records, registries and other forms of active and passive surveillance.

Baird et al. (2013) argue that the more adaptive programmes are generally correlated with more favourable stakeholder outcomes. However, these authors point out that their results should be treated with caution and suggest the initiation of prospective pilot studies of the AL concept in order to expand and refine their thinking.

An alternative to just shifting pre-launch work to post-launch work has been proposed in the form of Efficacy-to-Effectives (E2E) clinical studies (Selker et al., 2014). Under this approach, the effectiveness trial would commence seamlessly upon completion of the efficacy trial. The efficacy trial would be a standard randomised controlled trial. It would be used for regulatory review, once its methods and results have been approved (say by an external Data Safety Monitoring Board (DSMB)). This approval would also trigger the transition to an effectiveness trial. In E2E trials, results from the efficacy trial component would be used to design the effectiveness trial component, to confirm and/or discern associations between clinical characteristics and treatment effects in typical care, and potentially to test new hypotheses.

The effectiveness trial would be conducted in usual care settings using a more heterogeneous sample that is representative of the expected patient spectrum. Before initiation of effectiveness trials, regulatory agencies and the DSMB review the pre-specified transition and the differences between effectiveness and efficacy trials, including relaxed entry criteria and longer duration, to confirm that the plan is still appropriate. The E2E transition is not framed as an adaptive sequence (see Solution 2 for Challenge 1), although there may be circumstances in which adaptive and other features might be incorporated into the efficacy and/or effectiveness portions. Selker et al. (2014) highlight several barriers to the use of E2E trials; a solution could be the combination of the E2E effectiveness trial component with the initial authorisation stage of recent proposals for AL. Still, Califf (2014) argues that before this E2E vision can become a reality, numerous practical and conceptual barriers must first be overcome – although revolutionary clinical research methods that are now being piloted have the potential to help make E2E a reality.

Another not mutually exclusive option to AL and E2E to help shift work from pre to post-launch work is to pursue Performance-Based Risk-Sharing Arrangements (PBRSAs). Indeed, there is a significant and growing interest among both the payers and producers of medical products for these agreements. These arrangements involve a plan by which the performance of the product is tracked in a defined patient population over a specified period of time, and the level of reimbursement is based on the health and cost outcomes achieved (Garrison and Towse, 2013). PBRSAs represent one mechanism for reducing uncertainty at launch through greater investment in evidence collection while a technology is used within a healthcare system. These types of arrangements fall under a variety of names and categories: outcomes-based schemes, risk sharing agreements, CED, access with evidence development, PAS, conditional licensing, and managed entry schemes.

Solution 2: Recognition that studies are done for more than one country (i.e. avoiding duplication)

There is a common assumption in the literature that relative efficacy is constant and, therefore, generalisable across settings (Mestre-Ferrandiz et al., 2010). Thus, a pan-European approach to assess relative efficacy may be useful and feasible as most HTA/pricing and Reimbursement bodies use relative efficacy, with the following caveats:

- Methods used by member states to identify, include and analyse RCTs to assess relative efficacy are not similar. Particular issues are the selection of end points for consideration and the treatment of indirect comparisons, where head-to-head RCTs do not exist.
- Two benefits could include avoiding duplication of effort and raising quality of assessment in some member states – but without setting unrealistically high standards in terms of either trial end points or the need for direct head-to-head comparisons.
- The use made of a relative efficacy assessment seems, however, to be quite different across countries – especially to determine access to medicines. Thus, a pan-European assessment of relative efficacy may make no difference to the time taken to review a new medicine by a member state or to patient access.

Relative effectiveness is a function, not only of the attributes of the technology and target patient population (as relative efficacy is), but also of the performance of the healthcare delivery system and wider environmental factors. It will change over time and may be amenable to appropriately designed policy measures. The step from relative efficacy to relative effectiveness can be substantial and is likely to vary across health systems. There are

important differences across the member states HTA /P&R bodies when translating relative efficacy into relative effectiveness.

A key requirement to shift from pre to post-launch work will be to be able to generalise any effectiveness results post-launch. If this is not the case, there is a risk of requirements being imposed for multi-country post-launch data requirements. In the extreme companies would need to conduct post-launch studies in all member states, and in some cases different studies may be required for safety monitoring and for looking at effectiveness. This is simply not commercially or practically feasible in the absence of a transformation in the use of electronic patient records. We need better evidence on the factors driving relative effectiveness as that could help in determining the extent to which studies could be transferable from one country to another.

Solution 3: Increased confidence in observational (i.e. non-RCT) methods and researchers' capabilities

One barrier identified for greater use of relative effectiveness is the lack of confidence in both the scientific and regulatory communities that there are either sufficient methods or adequate data to ensure the validity of results of relative effectiveness studies (Mestre-Ferrandiz et al., forthcoming). These concerns reflect, amongst others, the shortage of trained researchers to conduct and analyse high quality pragmatic RCT and observational studies. Even within global companies, clinical development team preferences for RCT data leads to a general scepticism about the use of 'real world' data and pragmatic RCT or observational study designs. A further barrier in the wider implementation of more innovative, adaptive trial design approaches has been the lack of adaptive trial design experience among both internal development teams and external contract research organisations (Getz et al., 2013)

Industry is already playing a leadership role in helping to train future researchers. For instance, companies are partnering with academic institutions to create drug development research fellowships to expand training opportunities. Addressing these concerns about the wider use and confidence of non-RCT methods and researchers' capabilities is key.

What the UK should do (1): 'Coverage with evidence development' type arrangements through NICE and the SMC

NICE and SMC appraisal committees could consider expanding the use of CED to manage uncertainty when deciding whether a new product should be made available through the NHS. CED is characterised by restricted coverage for a new technology in parallel with prospective data collection when the stated goal is to provide definitive evidence for the clinical or cost effectiveness impact of the new technology. These schemes would enable patients to access a new treatment while relative effectiveness data on value are collected.

Alternatively, NICE and SMC could support a performance linked reimbursement type schemes, whose goal is to manage utilisation and control the cost effectiveness of a new technology in the 'real world'. These agreements are characterised by a reimbursement level (i.e. the net price per unit) for covered products that is linked to the measure of clinical outcomes. This scheme would enable tracking patient performance and produce scientific data on relative effectiveness. We have already seen a number of initiatives in the UK, although most recent PAS entail confidential discount schemes. However, there are examples to date illustrating two possible alternatives for performance linked reimbursement type schemes. First, comparability studies between competing medicines i.e. the medicine under the performance linked reimbursement type scheme is compared with an active comparator. The comparator can be a historic cohort of patients (such as in the case of the multiple-sclerosis agreement) or an active medicine (such as in the case of sunitinib versus imatinib for the treatment of gastrointestinal stromal tumours). Second, the outcomes for any one medicine are monitored, without comparing these to any comparator. Examples include bortezomib and getifinib (see case study).

In parallel to these initiatives, in September 2013, NHSE launched the Commissioning through Evaluation (CtE) programme for some treatments. Some existing treatments are not routinely funded by the NHS as the current evidence base is not regarded as yet demonstrating sufficient clinical and cost effectiveness for its routine use. In particular, this is the case of more specialised treatments where patient numbers may be too small to support research data requirements, treatment costs may be very costly, or there may be particular ethical considerations involved in exposing patients to an experimental treatment rather than one which is more routinely considered. CtE could potentially increase access to these types of treatments, since they could be funded whilst new evidence is gathered. This programme resembles a CED mechanism and can potentially provide important benefits to future patients. However, it could be further improved by extending its coverage to the NHS in Scotland, Wales and Northern Ireland. The first treatment to benefit of the CtE programme will be Selective Internal Radiotherapy (SIRT), a form of radiotherapy which uses radioactive beads to treat cancerous tumours in the liver. Around 220 patients a year are expected to be treated with SIRT as part of the CtE approach. Each of the services/treatments which are part of the CtE programme will be funded for between 1-2 years whilst new evidence is gathered.

What the UK should do (2): Ability to extrapolate NHS data to other countries

The NHS should consider how to generate further 'real world' data that can be extrapolated to other countries, making the UK one of the leading countries in the generation of post-launch data. This would also guarantee that the UK will remain an early launch market, enabling the UK to maintain and improve its global competitiveness. For this purpose, it is also essential that the UK uses the latest products available. If the UK can only generate data for older products, but newer products are more widely used in other countries, the data generated in the UK will be of little use in these countries.

What the UK should do (3): UK using latest products (standard of care in other countries)

The prompt adoption of the latest products as standard of care ensures that patients are given the access to the more innovative technologies and that these products can become the benchmark in future cost effectiveness evaluations. The NHS needs to make sure that the latest standard of care is used in the UK to provide all NHS patients with the best available treatments.

In addition, protocols for clinical trials do not always take into account a country's standard of care. If the protocol for a new medicine requires patients who originally failed a treatment that is actually not available in the UK, it will result in a low patient recruitment rates in the UK (Glancszpigel, 2009).

What the UK should do (4): Ability to do pragmatic trials pre-launch and post-launch

As pragmatic trials, both pre and post-launch, become more important, it is essential that the UK provides the right infrastructure to carry these out. This requires the appropriate IT infrastructure, skills and regulation and governance. For drug developers, integrated data delivers a much richer ability to not only assess outcomes but also to identify the right patient populations for clinical trials or expanded use studies. To this end, working in partnership is key. It is important that the data generated can be understood and used by pharmaceutical companies. This would reduce the costs for companies to interpret the data and integrate them into their developments programmes, making the UK an important hub for clinical research, both pre and post-launch.

The NHS should work with the industry to facilitate more pre-launch pragmatic trials to make relative effectiveness data available at or shortly after the launch of a new medicine. This would allow HTA bodies and payers to better understand the value of a new medicine and to take more informed decisions by reducing the uncertainty around the effectiveness of the medicine. The existence of relative effectiveness data at launch can increase the uptake of new medicines, providing important benefits to those patient subgroups who were not eligible for the new treatments if relative effectiveness information were not available. In addition, the earlier availability of effectiveness data increases the likelihood of early detection of rare adverse effects, benefiting the patients. The Salford Lung Study [see case study] is a good example of a pragmatic trial pre-launch.

The REACT pilot studies are a good example of what can be done post-launch, in real life settings [see case study]. They also highlight how the infrastructure is indispensable for their set-up.

Case study: REACT trials initiated within the GPRD

Randomised evaluations of accepted choices in treatment (REACT) trials are used to assess the effectiveness of products which are already on the market but where there is little evidence as to which has the better effectiveness in a live patient population for a specific indication, such as acute stroke. The attraction of such study designs is that they can potentially be conducted rapidly across large patient populations through access to electronic health records (EHR) with minimal patient disruption. A key requirement for such studies is that for treatments which are considered by the clinician to be equally effective, then the treatment chosen is done so randomly. Two feasibility studies have been initiated within GPRD; RETRO-PRO to examine the effectiveness of simvastatin compared to atorvastatin; and eLUNG: to examine the effectiveness of antibiotics compared to no antibiotics for exacerbations of chronic obstructive pulmonary disease. These studies are open label and non-blinded, with patients' progress monitored as usual in clinical practice, and these follow-up data extracted from the EHR.

There are a number of challenges to increasing the use of such studies in the UK, in particular issues associated with ethical and regulatory approval, patient consent, and quality, breadth and scope of current EHR. Over time as more REACT type studies are conducted these issues may be steadily addressed.

Source: van Staa et al., 2012

The Salford Lung Study

The Salford Lung Study is a GSK-sponsored study which aims to test the safety and effectiveness of a new treatment for asthma and Chronic Obstructive Pulmonary Disease (COPD), compared with standard medications used for these conditions, in a 'real world' setting in Salford, Manchester. It is the first, prospective, 'real world' study to be initiated in one geographical setting prior to marketing authorisation for this medicine, which has since been licensed in the UK and across the EU.

The importance of generating data in a 'real world' setting that is likely to be more representative of how the medicine may be used in reality is increasingly being recognised as an important complement to randomised controlled trials. It is believed that these studies may provide key insights into the potential utility and therefore the value of a medication in settings which reflect the reality of healthcare delivery.

Patients in Salford with asthma or COPD who agree to participate in the Salford Lung Study are being randomised by their GP, either to usual care or to the medicine being study and remain on treatment for 12 months. The final outcomes of this study will be measured through each patient's electronic health records which are collected at every visit.

The study is a collaboration between GSK, North West e-Health (NWeH), the University of Manchester, Salford Royal NHS Foundation Trust, NHS Salford's local general practitioners, and local community pharmacists and is sponsored by GSK.

The initiative draws on Salford's e-Health records infrastructure, a clinical information system that provides a single, integrated electronic patient record across primary and secondary care. This will ensure patients are closely monitored over the course of the study, yet with no intrusion into their everyday lives.

What are the challenges for the NHS?
"The most important challenge was the need to develop an efficient, integrated, multidisciplinary team, who all came from different working cultures, and ensure there was a common understanding and ways of working. In addition, the amount of training and support required when setting up research naïve sites should never be underestimated".

"Another significant challenge has been that primary and secondary data and indeed pharmacy data are not linked. North West eHealth has had to work hard to link the data and Salford is one of the few places in the UK to have the capability. If the UK is to become a key player in the generation of 'real world' data, we will need the ability to link these data sources in real time." GSK, 2014

Source: GSK; ABPI, 2013

Challenge 5:

The potential disconnect between regulators and payers/HTA bodies evidence needs

There is a potential disconnect between what regulators and payers/HTA bodies expect to see in terms of evidence to meet their information needs, for instance, what constitutes appropriate comparators and whether surrogate endpoints are valid markers of efficacy (Garattini and Bertele, 2009; Shah et al., 2013).

Non-inferiority trials for a marketing authorisation applications will not give payers evidence that the medicine under evaluation is more effective than alternative relevant treatment options. The disconnect is driven in part by the different remit of regulators and payers/HTA bodies; HTA bodies are asking a somewhat different question from that the regulator has asked. The EMA explicitly acknowledges this potential disconnect: "In contrast to the benefit/risk assessment carried out by regulators, HTA bodies compare the relative effectiveness of medicines and take their financial cost into account. This can lead to differences in the types of studies needed to support the assessment carried out by regulators and HTA bodies." The European Commission gave the political mandate to the EMA to start interacting with HTA bodies in October 2008 (EMA, 2011).

In addition, there might be differences in evidentiary needs across different HTA bodies in Europe. For instance, the comparator in a multi-national trial may represent standard therapy in some European countries but not in others. Other differences include the systematic use, or not, of cost effectiveness analysis and treatment of surrogate measures (Shah et al., 2013).

These two factors add to the complexity of clinical trials, an important driver of rising R&D costs over the last decade.

Solution: Greater harmonisation of regulator/HTA body requirements and within HTA body requirements (i.e. greater coordination)

a. EMA and HTA bodies at European level

Both regulatory bodies and HTA bodies are willing to offer pre-launch scientific advice to companies to assist them in planning clinical development programmes. A number of regulatory (including the EMA) and HTA bodies are willing to participate in joint meetings with companies and offer parallel advice. This is the case in England and Sweden (Tapestry Networks, 2010; 2011; Expert group on innovation in the regulation of healthcare, 2013). Some health authorities have even established consulting arms to provide guidance to manufacturers about the type of evidence needed for optimal reimbursement outcomes. This includes NICE.

However, the advice from regulators and HTA bodies, set out in separate subsequent correspondence, may not be aligned. It is uncertain if this could extend over time to offer companies advice on post-launch studies as well as pre-launch studies. However, this possibility introduces an additional complexity into parallel advice. It would need to cover pre and post-launch trade-offs. But it would provide a framework for dialogue between HTA bodies and the EMA. One possibility is for the EMA to consult with HTA bodies before it finalises the exact nature of any post authorisation efficacy studies it requires.

Case study: The IMI GetReal initiative: Incorporating real-life clinical data into drug development

GetReal is a public-private partnership, under the auspices of IMI, between key European stakeholders and leading research groups, including the EMA, the Dutch reimbursement body CvZ, and the International Alliance of Patients' Organizations (IAPO) that covers patient organisations all over the world. GetReal creates impact by developing a set of tools, decision frameworks, methods and insights to include real clinical data in drug development.

The GetReal consortium aims to improve the efficiency of the medicine development process by better incorporating real life clinical data into drug development and to enrich decision making by regulatory authorities and HTA bodies through:

- Bringing together regulators, HTA bodies, academics, companies, patients and other societal stakeholders
- Assessing existing processes, methodologies, and key research issues
- Proposing innovative (and more pragmatic) trial designs and assessing the value of information
- Proposing and testing innovative analytical and predictive modelling approaches
- Assessing operational, ethical, regulatory issues and proposing and testing solutions
- Creating new decision making frameworks, and building open tools to allow for the evaluation of development programmes and use in the assessment of the value of new medicines
- Sharing and discussing deliverables with, amongst others, pharmaceutical companies, regulatory authorities, HTA/reimbursement agencies, clinicians and patient organisations
- Developing training activities for researchers, decision makers and societal stakeholders in the public and private sector in order to increase knowledge about various aspects of relative effectiveness

Source: http://www.eortc.org/sites/default/files/IMI%20Get%20real.pdf

b. HTA bodies within Europe

There have been a number of initiatives at European level, including the High Level Pharmaceutical Forum process which initiated the reflection on pan-European approaches to relative efficacy/effectiveness, the 2009 Swedish Presidency Initiative for cross border collection of observational data, the European League Against Rheumatism example of such a cross-border initiative in the field of drugs for rheumatoid arthritis, the Medicine Evaluation Committee group of member state P&R bodies, and the EUnetHTA programme. For example, the work of EUnetHTA Joint Action 2 includes the piloting of a Rapid Relative Effectiveness Assessment for pharmaceuticals which seeks to explore the potential for greater coordination and sharing of both "rapid" (at launch) HTA assessments for medicines across payers and HTA bodies within the EU.

What the UK should do: UK relevant bodies to be a leading force in shaping the EU environment

NICE is involved in the initiatives at European level which focus on HTA; for example, in the IMI "Get Real" consortium. The NHS needs to ensure that recommendations from this project, that can enhance the UK science and clinical research base and improve the information available for patients, clinicians and NICE are acted upon. To attract clinical trials to the UK that require a 'real world' setting, the NHS would need to ensure that it is generating and efficiently recording real life clinical data about the effect of treatments on its patients. This requires trained and skilled staff and the adoption of new technologies/processes. If the UK does not act, other countries will, and they will get the research and evidence to improve the quality of patient care.

Both the MHRA and HTA bodies across the UK need to proactively engage with European activities to develop workable early access schemes and innovative pathways such as adaptive licensing, as well as continuing to participate in programmes to offer parallel scientific advice to companies as they plan their clinical trials.

In addition, companies should be aware that MHRA/NICE offer a joint scientific advice service so that companies can consider medicines regulation and HTA issues in parallel.

Conclusion

Five challenges have been identified in the way that medicines are currently, and possibly will be in the future, researched, developed and used. To overcome these challenges, eight possible solutions have been identified. Some of these solutions are already being acted upon by the relevant stakeholders. Others require initial steps to be taken.

For the UK in particular, 10 actions have been suggested, focusing on what the UK should do to ensure it can maintain a leading environment for R&D, both pre and post-launch.

The premise underlying these recommendations is that good research and patient access to new medicines go together - especially because of the importance of 'real world' evidence pre and post launch. Working in partnership should increase the competitiveness of the UK and deliver better health for all.

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Definitions

Adaptive design in clinical trial: a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study. Analyses of the accumulating study data are performed at prospectively planned time points within the study, can be performed in a fully blinded manner or in an unblinded manner, and can occur with or without formal statistical hypothesis testing. The term prospective here means that the adaptation was planned (and details specified) before data were examined in an unblinded manner by any personnel involved in planning the revision. (FDA, 2010)

Adaptive licensing: the adaptive licensing approach, sometimes called staggered approval or progressive licensing, is part of EMA's efforts to improve timely access for patients to new medicines. It is a prospectively planned process, starting with the early authorisation of a medicine in a restricted patient population, followed by iterative phases of evidence gathering and adaptations of the marketing authorisation to expand access to the medicine to broader patient populations. AL seeks to maximise the positive impact of new medicines on public health by balancing timely access for patients with the need to assess and to provide adequate evolving information on benefits and harms so that better informed patient care decisions can be made. (EMA, 2014; Eichler et al., 2012)

Comparative effectiveness research: "conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat and monitor health conditions in 'real-world' settings. The purpose of CER is to assist consumers, clinicians, purchasers, and policymakers to make informed decisions that will improve healthcare at both the individual and population levels." (IOM, 2009)

Electronic health records (EHRs): collections of patient health information generated by one or more meetings in any care delivery setting. An EHR typically includes patient demographics, progress notes, problems, medications, vital signs, past medical history, immunisations, laboratory data and radiology reports.

Health technology assessment: a form of policy research that examines short and long term consequences of the application of a healthcare technology. The goal of HTA is to provide policymakers with information on policy alternatives. For any given technology, properties and impacts assessed may include technical properties (this is particularly germane for sophisticated equipment), evidence of safety, efficacy (including patient reported outcomes), 'real world' effectiveness, cost, and cost effectiveness, as well as estimated social, legal, ethical, and political impacts. Thus, HTA is conceived as being much broader than is typically true of health and economic outcomes research of a healthcare technology (http://www.ispor.org/terminology/default.asp).

Post Authorisation Efficacy Studies (PAES): studies which are undertaken after a medicine has been authorised with the purpose of providing more information on the efficacy of the product within the authorised indications. Those studies are not an entirely new feature, already now post-authorisation efficacy studies may be conducted. However, with the new pharmacovigilance legislation those studies are formally recognised. It is clarified that marketing authorisation holders can be obliged to conduct such studies by imposing that obligation as a condition to the marketing authorisation.

Post Authorisation Safety Studies (PASS): any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

Protocol: plan detailing the methodology of a clinical trial.

Relative effectiveness: the extent to which an intervention does more good than harm compared to one or more alternative interventions under the usual circumstances of healthcare practice." (HLPF, 2008)

Relative efficacy: the extent to which an intervention does more good than harm compared to one or more alternative interventions under ideal circumstances, i.e. under clinical trial conditions. (HLPF, 2008)

Risk management system: a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of these interventions. A risk management system for an individual medicinal product or a series of medicinal products can be presented to Competent Authorities in the form of an EU Risk Management Plan.

Specialty products: medicines that treat specific, complex chronic diseases with four or more of the following attributes: initiated only by a specialist, require special handling and administration; unique distribution; high cost; warrants intensive patient care and might require reimbursement assistance. These products are used for the following therapy areas: oncology, autoimmune, inflammatory, respiratory, multiple sclerosis, HIV and non-HIV antivirals, as well as genetic diseases, such as cystic fibrosis. (IMS, 2013)

Stratified/personalised medicine: use of genetic or other biomarker information to improve the safety, effectiveness, and health outcomes of patients via more efficiently targeted risk stratification, prevention, and tailored medication and treatment management approaches. (Personalized Medicine Special Interest Group (PM SIG) of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR))

Ultra-orphans: there is no formal definition of ultra orphans (which is a UK term) but two (unofficial) definitions tend to be used, one by NICE (UK prevalence of less than 1 in 50,000) and one by AGNSS (usually not exceeding 500 patients for England as a whole).

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