Vermilion Life Sciences

Exploring new connections and alternative approaches

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Bringing medicines to *life*

Reengineering medicines development

A stakeholder discussion document for cost-effective development of affordable innovative medicines

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Foreword

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The ABPI is committed to ensuring that the UK is an ideal environment for the research and development of innovative medicines. It is widely recognised that the traditional model of drug development is unsustainable. As we develop increasingly complex and personalised medicines, significant change is needed to reverse the escalating costs and timelines associated with development, and maintain the affordability of innovative medicines. The ABPI believes that the UK now has an extraordinary opportunity to capitalise on recent trends and enablers to lead the world in 'reengineering medicines development'.

There are several initiatives already beginning to change the medicines development environment. The EMA Adaptive Pathways initiative and the MHRA's Early Access to Medicines Scheme demonstrate a move towards more flexible pathways for regulatory approval. The publication of Personalised health and care 2020 shows the continued commitment of the UK government to increasing the use of health data for patient benefit. Together with the UK's unique healthcare system and the international reputation of the National Institute for Health and Care Excellence (NICE), the UK is ideally placed to lead drug development towards a more sustainable future – a future dependent upon stratification, real world studies and close stakeholder partnerships. We hope that this discussion paper will drive a significant change in medicines development, building on these, and other, initiatives to create a UK environment ripe for investment in sustainable drug development. The government's timely 'Innovative Medicines Review' should further propel increased innovation in healthcare in the UK.

This discussion paper proposes a methodology to substantially reduce the timelines and costs associated with late phase studies – to bring benefit to all stakeholders, and most importantly bringing innovative medicines to patients more quickly. This vision will only be achievable by working in deep partnership with patients, healthcare providers and practitioners, Health Technology Assessment bodies and payers, regulatory authorities and the pharmaceutical industry.

We hope this paper will be the starting point for discussion and collaboration on a new model of stakeholder partnership to move together towards a truly 21st-century model of drug development in the UK.

Executive summary

The challenges, costs and risks of medicines development are well documented. The cost of successfully developing a new medicine has been recently estimated at $2.6bn, which includes the substantial costs of failure during development. Increasing pre-approval requirements based on concerns of predictability for patient safety, together with increasing needs for cost-effectiveness data, have extended the time and cost of development and slowed adoption of use. This has in turn reduced the time window for return on ever-increasing investment. As such, companies have sought to maximise returns on successfully approved medicines to permit continued investment in R&D. This has further increased cost-effectiveness challenges as well as affordability concerns.

This document proposes a methodology to substantially reduce the time and cost of late phase studies, by replacing the dependence on randomised controlled trials that do not reflect clinical practice. Novel, matched case controlled studies which include real world data of patient relevance can utilise health databases to more quickly identify and recruit subjects, and allow data capture and analysis in real time. Adaptive designs, with prospective and in-stream stratification, can increase targeting and further personalise medicines development. Time and cost savings are achieved through expedited recruitment, reduced study complexity and use of fewer investigator sites.

A blended study methodology increases the relevance and correlation of late phase development to normal clinical use. This reduces the lack of predictability of the randomised clinical trial. Incorporating real time analysis allows rapid hypothesis testing and an ability to file fast or fail fast, when statistical significance or thresholds are reached. This substantially increases study effectiveness and reduces the inefficiency and cost of development activities. With successful early filing, a targeted indication, based upon the patient population studied, is expected. Continuation of these studies through the review and post-approval periods subsequently allows adaptation of the population or the labelled indication to reflect the data generated.

The inclusion of real world patient data increases relevance for HTA, pricing and reimbursement purposes. Early agreement of the utility of these measures, through construction of value indicator scales, enables greater predictability of cost-effectiveness at defined price points. Modelling this against the target product profile can inform company investment decisions based on likely value and return, but will ultimately be determined by the data generated. As substantial time and cost savings can occur, greater flexibility to adapt the price point upon these scales to achieve cost-effectiveness should be possible. As further evidence on efficacy, safety and health outcomes accrues through continuing longitudinal study, the value proposition would evolve and be measured against these value indicator scales. This would allow ongoing adaptability of labelling and pricing to reflect the value of the medicine in its use and its environment.

Recent trends in stratified medicine, database use, analytical methods and regulatory adaptation enable this approach. For this methodology to become a reality, however, greater partnership and alignment is needed by all stakeholders. The UK, having a unitary healthcare system with a potentially integrated database, has a significant advantage to take the lead in designing and developing such studies and attracting inward investment. The UK should aim to set standards for wide application and implementation in the light of other countries considering similar approaches. This document discusses the opportunity for stakeholder alignments to deliver the promise of speed, cost-effectiveness and personalisation of medicines development.

Introduction

The development of a new medicine costs approximately $2.6bn and is accelerating from the 2003 estimate of $800m ($1bn inflated for 2014).[1] This cost reflects not only successful development, but also the significant cost of pipeline failures. These estimates are driven by the increasing size, complexity and duration of Phase III studies to satisfy increasing approval and reimbursement requirements. This increased scale has been driven by safety concerns and a desire to demonstrate clinical outcomes. Concerns regarding adverse events that are not detected pre-approval, or whose frequency or severity increases in clinical use, have increased pre-approval requirements,[2] as have concerns that surrogate endpoints do not translate to meaningful outcomes. These are valid concerns, but increase the costs of late phase failure whilst increasing post-approval commitments.

These increases in post-approval requirements highlight, however, the fact that despite more extensive Phase III programmes, reassurance of clinical use does not follow. The increase in Post Approval Safety Studies (PASS) and Post Approval Efficacy Studies (PAES) also highlights the artificial distinction between the randomised controlled trial (RCT) and clinical reality. Post-approval requirements are increasingly more stringent, particularly in Europe. While post-approval, real world pharmacovigilance monitoring was introduced in recognition of this distinction, and in an attempt to streamline the pre-approval burden, very limited reduction of pre-approval requirements has occurred, whereas substantial additional post-marketing requests continue.

The RCT has been the gold standard for medicines development, and its scientific value is not in question. Extrapolating evidence of effectiveness to a broader population, however, is a limitation. This leads to uncertainties in pricing, reimbursement and HTA reviews, further delaying adoption and uptake of new medicines. Double blind, multicentre Phase III RCTs do not represent the population at large, are lengthy and use resource ineffectively. This underlies their considerable cost, but is the reality and part of the reason for unsustainability of the current system. Including health outcome and cost-effectiveness measures in ever more complex development plans further increases pre-approval time and cost. Paradoxically, these increased requirements directly inflate the costs of approved medicines, making affordability and cost-effectiveness even more challenging.

The lack of evolution of medicines development from a twentieth-century model is anachronistic in the twenty-first century, where personalisation, stratification and real world data are increasingly relevant. This paper examines current trends and opportunities and proposes reengineering medicines development by capitalising upon recent trends and enablers. For change to occur, however, we propose that a new model of stakeholder partnership is required.

Recent trends

Personalisation of care is now a reality through biomarker stratification

In attempts to reduce development risks and costs of late-stage failure (many of which are now failures of benefit: risk in the longer term, or failures of competitive patient-level benefit or differentiation) many companies have invested in translational medicine and biomarker development to increase confidence and probability of success. These seek to define predictors of efficacy and safety, or identify and stratify specific populations with improved benefit risk. These strata may be demographic or genomic or a combination of a variety of background and environmental factors.

The newer sciences of genomics and metabolomics provide increasingly sensitive biomarkers for stratification and personalisation of medicines in development and use, and improve the relevance of the study to the clinical population. This can improve benefit risk assessment for earlier decision making in defined populations, with commensurately greater success rates. Prospectively determining treatment strata through genomics and biomarkers builds on the existing detection of specific metabolic variations as well as the targeting of oncology therapies. The plan by Genomics England[3,4] to type 100,000 genomes in rare diseases and cancers is a significant step to studying targeted novel therapies based upon both prospective and retrospective markers to determine response. President Obama, in his 2015 State of the Union address, has made a similar 'Precision Medicine' pledge.[5] UK Biobank[6] and the MRC-NIHR National Phenome Centre[7] complement this further by investigating phenotypic strata, building a picture of complex polygenic variations, phenotypic markers and environmental interactions. These will further personalise care and therapy selection, as will patient demand for personalisation and prevention, through increasing numbers of patients holding their own genomic data via companies[8] constructing patient-held data plans.

Regulatory authorities are investigating early approval and access paths

Reducing development risk through regulatory interaction is a common expectation. FDA End of Phase II and EMA Scientific Advice meetings are well established and set approval expectations. In many cases, however, greater certainty of efficacy and safety by heightening pre-approval requirements is requested. For a broader view, joint and parallel Scientific and HTA Advice is now available (although as a relatively new process it has had limited uptake), but it facilitates early consideration of HTA requirements to inform pricing decisions. Because of the nature of the RCT as a backbone for regulatory approval, however, HTA requirements are often incremental assessments, further increasing the time and cost of development.

While post-approval measures provide ongoing scrutiny and real world data, there can be difficulties interpreting these assessments if access or uptake is slow. Large RCTs remain part of regulatory requirements, and prevent timely clinical use of potentially promising therapies, while eroding patent life and reward for investment.

Recognition of these challenges has prompted regulatory initiatives to speed the review for medicines that address significant unmet or life-threatening medical needs, leading to conditional or restricted approval with proscribed follow-up. FDA's Breakthrough Designation,[9] EMA's Adaptive Licensing / Adaptive Pathways[10] and MHRA's Early Access to Medicines Scheme (EAMS)[11] are all such approaches that have demonstrated a willingness to appreciate and confront some of these challenges. Dialogue with sponsors has been initiated to assist in rapid assessment and, if appropriate, tiered levels of approval with possibilities for patient stratification.

The recent publication from multiple stakeholders on Adaptive Pathways[12] has further clarified this concept to accelerate and adapt medicine development, approval and use in a progressive manner. It provides a pathway for tiered levels of confidence and licensing, with continued monitoring and development while blurring the concept of approval as a 'finishing line'. Importantly, there is recognition that the level of confidence can increase and decrease over the life cycle, which may lead to regulatory label expansion, restriction or even withdrawal. It also helpfully includes the concept of coverage, and its ongoing examination for cost-effectiveness as new evidence is generated. Different RCT models, including

stratification, are discussed to propose outcome studies that are reported and approved on surrogates, but continue to outcome measurement during a restricted post-approval period. The role of observational studies as a complementary post-approval data source to RCTs is discussed, but concern is raised about the overall strength of observational evidence.

IMI's focus on Medicines Adaptive Pathways to Patients (MAPPs) as a novel investigation that blends real world data may further build upon these aspects and have benefit across Europe. Complementing this with the IMI Electronic Health Records for Clinical Research[13] (EHR4CR) gives a sense of the possibilities in both study recruitment and feasibility, and may provide a platform to incorporate wider use of adaptive designs.

The MHRA's EAMS has at the time of writing had three Promising Investigational Medicine (PIM) designations assigned;[14] however, as yet the additional benefit from this approach is uncertain. Ten of 34 applications for EMA's Adaptive Pathways have been granted further discussions[15,16] based upon severity of the disease, an iterative approach to population expansion, engagement of HTA bodies and use of real world data post-approval. The next phase of this exercise begins in March 2015.

In the USA, several breakthrough designations have been adopted, with benefits of an accelerated pathway put in place. Notably, the approval of blinatumomab occurred five months earlier than expected.[17] More recently the US Energy and Commerce Committee has released the 21st Century Cures white paper. There are initial proposals in the discussion document[18] on improving use of real world data, health databases, stratification and adaptive trial design to focus the role of the US as a global innovation centre. While it is unclear how these proposals will be enacted, the target for legislation is the end of 2105. No mention is made of international standards, but they will be an important aspect for this, and other proposals, to be attractive and tractable.

Electronic health databases allow adaptive analyses but privacy concerns remain

The recent launch of the Farr Institute may provide some solutions to address concerns of observational study robustness. Their remit is to deliver high-quality, cutting-edge research, linking electronic health data with other forms of research and routinely collected data. This builds upon the experience and benefits of CPRD as well as building capacity and robustness in health informatics research.

The pharmacovigilance utility of CPRD is widely recognised, whereas the ability to test other associative hypotheses is less well used, but no less useful. Expanding these capabilities, through integrating the healthcare platform via HSCIC and care.data, has been postponed because of concerns of public trust in data privacy, which underlines the complexity of this area and the need for careful explanation and consent in any use of data. Nevertheless, the potential for alternative data generation models exists in such a system.

Capitalising upon electronic healthcare records in the NHS links to the work of the National Information Board (NIB) and their recently announced *Personalised Health and Care 2020* report.[19] The strategic priority recommends data and technology partnership with industry, and research across the care sector with investment to exploit the information revolution. It explicitly recognises the potential of real world evidence for developing and adopting new treatments. The ambition for England to be a leading digital health economy to address long-term public health is clearly stated, as it is to support research, particularly in the areas of genomics.

The NHS *Five Year Forward View*[20] and the NHS *Forward View Into Action*[21] both complement the NIB's position. These recognise opportunities to deliver new models of care through digital approaches, the work of AHSNs and research partnership with industry and other sectors. With the AHSN's remit in healthcare systems integration and adoption of innovation, there is a call to realise the potential to implement the NIB's approach. Several geographic regions[22,23] have stated their intentions to integrate records for research and healthcare purposes, with potential to facilitate the work of the AHSNs and build on the existing NIHR/NOCRI Clinical Research Network for further outreach.

Database approaches have become more attractive because of the advent of big data analytics. The increase in artificial intelligence computing, as seen with IBM Watson, to examine multiple associations at speed, has led to greater interest in deep analysis of collected data. Coupled with increasing sources of data from smartphones, wearable devices and real time uploads, the ability to develop and test hypotheses with real world data from multiple sources in real time has provided incentives for technology companies to invest in healthcare. Reports from Deloitte[24] and McKinsey[25] have discussed how new data approaches have the ability to reshape pharmaceuticals from discovery to commercialisation. Given the challenges of clinical development, this is an area highlighted as a major opportunity for change by both reports.

Pricing, cost-effectiveness and affordability concerns lead to a vicious cycle of delays

Despite innovative science leading to effective therapies, approved new medicines face delays in uptake and use. Assessment of cost-effectiveness based upon premium pricing leads to access restriction. While premium pricing is a result of a desire to earn a return on high-cost, high-risk R&D and fund its reinvestment, the resultant cost-effectiveness limitation creates a vicious circle of delay in adoption and financial return, with further escalation of pricing. This adoption and affordability dynamic leads to individual discount negotiations that are not transparent as they protect the public list price. Even in countries with private insurance schemes, the affordability of high-price medicines is increasingly of concern, with curative Hepatitis C therapies the most recent examples.[26]

One response to challenges in medicines adoption has been NHS England's Cancer Drugs Fund.[27] While this has improved cancer medicine availability, it is a temporary solution that addresses the symptoms of medicines development rather than the problems. While the UK is supportive towards life sciences innovation and generally accepts adoption of cost-effective technologies, closures of UK research and development facilities have caused concern. This is important to recognise, given the global nature of the industry. The UK Government's Office for Life Sciences (OLS) has acknowledged these challenges from the perspective of the impact on patient care, and from that of industry. The OLS *Innovative Medicines and Medical Technology Review*[28] provides the prospect to seek mutually beneficial changes. With the above regulatory initiatives and the outcome of the NICE review in February 2015,[29] these provide an opportunity to take a lead in partnership working towards shared objectives.

While these promising pilot initiatives are welcomed, they are incremental and somewhat piecemeal. Incremental changes to the current model will, however, not improve time and cost concerns sufficiently to rescue this unsustainable model. To transform development and improve healthcare, a disruptive change based on new partnerships is required to revitalise the development of novel medicines at a reduced time and cost. All stakeholders should take the opportunity to discuss and agree a shared objective for medicines development and use. Collectively devising ways to achieve this objective to reengineer medicines development could deliver more affordable medicines more quickly to improve public health.

Partnership working in pilots has shown initial promise

The work of NEWDIGS via the Janus project[30] has examined the potential of novel approaches to development in both native and stratified populations. Proposing adaptive approval strategies with early multi-stakeholder input has been discussed to facilitate development, approval, reimbursement and adoption over the entire product life span. Other work has examined database identification of patients to improve recruitment speed and thus reduce the cost of clinical trials. A reduction of 30% in recruitment times and study sites was modelled.[31] Further modelling recognised the need for a conjoined approach and novel tools to enhance benefit through stratification, but noted that regulatory and commercial barriers to successful implementation remain.[32] Nevertheless, partnership approaches provide hope for a model of faster, less costly development that is more predictive of clinical reality. A continuum of relevant pre- and post-approval studies can thus lead to flexible licensing, pricing and reimbursement.

This document sets out proposals for discussion between stakeholders to reengineer medicines development to improve and protect public health.

Opportunity

A partnership approach has the potential to reduce the time and cost of development, while improving clinical relevance of studies and their assessment of cost-effectiveness. Improving public health through appropriate uptake of medicines at lower cost and improved cost-effectiveness, without any reduction in development standards or scrutiny, is an important incentive to develop new methodology. Real time database utilisation, new analytical methods and adaptive approaches can underpin this.

Blending observational elements with aspects of RCTs can more reliably reflect real world clinical use, while simultaneously increasing robustness and relevance of evidence generation. Using integrated databases for patient identification and recruitment across care pathways can substantially reduce recruitment time, study size, complexity and costs, while development of a dispersed investigator network using geographical hubs permits access to a broader patient cohort, reducing non-recruiting centres. 'Big data' analytics can be employed on remotely monitored biometric data in real time, to reduce patient inconvenience and increase study retention. This increases study efficiency through patient management within a geographic investigator network.

Prospective and retrospective stratification can augment such studies. A specific population can be identified for targeted therapy in an adaptive design and may further shorten the development timeline. In addition, stratification may change the benefit risk profile of a project to be more beneficial in a selected population. As such, an asset of marginal benefit may become more attractive to develop, given lower investment and faster time to decision.

A partnership approach that builds on existing scientific advice processes to agree, in principle, to development plans and their main measures before study initiation, can set minimally acceptable thresholds of efficacy, safety and effectiveness for comparison to expected target product profiles. There should be no reduction of regulatory governance or scientific rigour in assessment of these measures as they are indicators of suitability for approval or futility. Similarly, the indicative values of derived health benefits should be considered as go/no-go criteria based on the emerging profiles through both biometric measures and specific Quality of Life (QoL) tools.

Application of these measures in real time allows projects to fail fast or file fast if pre-defined decision thresholds are met. Additionally it facilitates adaptive study designs based upon the emergence of data patterns. This allows amendments to selection criteria, assessment parameters, sample size or comparators. Should a project progress to filing for approval, longitudinally extending studies provides essential follow-up data to expand or restrict use as appropriate, and can be part of the regular vigilance assessment for new medicines. It can also provide a seamless continuous HTA and pricing/reimbursement process, completing a flexible, phased, life cycle approach to medicines development, approval and pricing.

Breaking the cycle of increasing R&D cost is a key factor. It leads to price escalation with commensurate reduction of cost-effectiveness, which in turn delays adoption and further increases cost. Making savings in study time and cost, to permit earlier filing and HTA assessment, should lead to greater price flexibility even in stratified or restricted approvals. As evidence accrues through post-approval continuation of studies, the value proposition will change based on the evidence generated. The price paid for a medicine should thus adapt to account for the value it brings. Ultimately greater cost-effectiveness and affordability should result. With lowered development costs, a reduced price can maintain profitability, increase development portfolio cost efficiency, and allow the progression of a greater number of promising projects at reduced cost.

The potential to integrate care pathways and database records within the NHS gives the UK an opportunity to set a new regulatory standard and take a lead in enhancing patient care through medicines evaluation and uptake. Other countries and health systems are considering similar data approaches, albeit from a less integrated starting point. Setting global regulatory standards for wider applicability, including utilisation of data generated substantially in the UK at improved speed and cost, would be a major incentive for UK life science investment.

Reengineering medicines development – a methodology proposal

A reengineered medicines development model can build on current trends and opportunities to reduce time and cost while increasing clinical relevance. Improved real world data analytics from health databases would permit faster decision making to reduce futile R&D spend, increase study cost-effectiveness and provide a greater oversight pre- and post-approval. These technology trends are, however, only an enabler of a new approach. Stakeholder partnership, receptivity and flexibility to new methods and an ongoing relationship are the catalyst for success. An outline proposal follows.

Scenario planning includes detailed patient input during Phase II conduct

While an asset is in Phase II, initial safety, efficacy and dose-ranging should be determined against placebo and an active comparator. During Phase II the ultimate patient population should be planned for, to support real world assessment in lieu of, or in parallel to, Phase III.

Scenario planning for positive data from Phase II should include discussions with regulatory agencies, patient groups and HTA bodies to agree data requirements. Early partnership with patients, through disease-specific groups or medical research charities is essential to incorporate their needs. This is particularly important for measures of QoL, daily activities and disease-specific burden. Such input at this stage can help determine if the asset is of real interest for further development. The methodology to record and assess these factors should be driven by patient insight, and where possible should use validated measures. With new assessments, however, there is the possibility that they may need validation in parallel. Given the likely acceleration of development, requirements such as toxicology, CMC, scale-up and stability – normally conducted during Phase III – may need acceleration, being performed at a higher-risk phase of the project.

Full development decisions are based upon multiple stakeholder agreements

With positive Phase II data, patient insights and further data generation should be discussed with regulatory, payer and HTA bodies, together with patient representatives as independent active participants. These meetings should agree study plans and measurement parameters to evaluate incremental effectiveness and value, based upon the expected product profile. For each parameter, a scale establishing the value 'headroom' achievable for the level of benefit seen should be developed. Assessing value directly against changes in these parameters, will allow modelling of absolute and relative effectiveness. Value indicator scales that link to QALY models would represent the value gain from the profile and QoL measures, and can be modelled for the most likely, upside and minimally acceptable profile. 'Subtraction' factors for varying impacts of safety liability can also be applied. The resultant profiles can model price sensitivity and expected levels of cost-effectiveness. The views of the patient representatives on QoL and personal health impacts are important to validate any assumptions.

The output of such meetings should be a non-binding agreement in principle to this approach, with value indicator scales embedded in plans. Analysis plans should include real time analysis, and formal interim review points based on recruitment or event numbers. Threshold levels can be documented for relevant parameters that might trigger earlier adaptive 'in process' progression or termination decisions. Requirements for specific age, gender, ethnic or other demographic groups and those with comorbid disease can also be agreed. Depending upon their prevalence, these may be incorporated into the study plan, or used in specific interventional studies if needed.

Agreement of this approach allows a sponsor to review the likely efficacy and safety profile at the selected doses emerging from Phase II, and the expected value scenarios through early payer feedback. The full development progression decision can then be taken with clear insight into the value achievable from the

project. It can be reviewed against expected pricing and cost-effectiveness estimations in key countries based on the probability of uptake at a desired price point. Defining and agreeing these parameters and the interpretation of them is the key to a successful programme.

Regulatory requirements for different country participation will vary, and discussions on the applicability of this new approach to individual countries will be needed. Meeting with a variety of national and regional regulatory, payer and HTA bodies will provide breadth of insight and understanding as well as informing and assisting decisions regarding validation and use of tools, database selection, integration and applicability for data utilisation. As discussed previously, there is likely to be a degree of convergence in new thinking to facilitate this, but ultimately design and adoption of a new regulatory standard should be the aim.

If the sponsor decides to progress to Phase III based upon the agreements in principle, study feasibility using appropriate databases and/or traditional RCTs can be conducted in appropriate countries. Additionally, based on validated or experimental data, pre-specified biomarkers or genotypes can be selected to determine whether identifiable patient strata demonstrate differential efficacy or safety.

Phase III feasibility utilises database-driven recruitment and matched case control design

It has already been demonstrated that use of healthcare databases can identify, and in theory, source eligible trial participants with a substantial saving in time. As referenced above, estimates of 30% have been determined for recruitment into a standard RCT. Blending this approach with real world study designs would provide further benefits. While patients would still need to be identified and consent to participate, the selection criteria could be less restrictive and, wherever possible, study procedures less onerous. Overall study size could also be reduced, if a novel approach to placebo and active comparators was employed, to reduce patient numbers without reducing the size of the safety database for the investigational medicine.

Given the utility of healthcare databases to track and identify subjects, alternative randomisation and comparator approaches can be used. The administration of open label or single blind Investigational Medicinal Product (IMP) to all eligible consenting database subjects is possible. Undertaking this in an identified geographic cohort enables cluster randomisation, with a matched case control comparison of patients receiving the IMP to those who are not. Those not receiving IMP are the comparison for standard of care (in effect a placebo). Depending upon treatment pathways and uptake of therapeutic alternatives, matched case control methodology can simultaneously determine relative effectiveness versus one or more active comparators.

This simplification of comparator use can achieve significant time and cost savings in recruitment, as well as IMP preparation. In addition, if new medicines are approved and adopted in the health system after study start, they can be utilised as comparators in the same way, with a flexibility and efficiency that is not possible in a traditional RCT design. If, however, there is a low level of uptake of a comparator, the ability to identify control numbers in sufficient quantity may challenge the robustness of the analysis.

The utility of comparator data is dependent upon the strength of the database and the parameters it collects routinely. Additional consent may be required for subjects not receiving IMP, but undergoing additional data collection for healthcare utilisation and QoL. These measures should be as objective as possible to support data quality and GCP. To prevent bias, data can be collected via a separate standard of care protocol, possibly in a different geographic region. In both IMP and matched control subjects, wherever possible routine healthcare visits should be used to record data. These can be augmented through real time, remote mobile health applications to minimise patient and HCP input and reduce study visits and costs. This will increase subject retention as well as data objectivity. Specific data quality processes can be agreed for wearable or smart tools that can be validated for the adoption of new scales. These scales can be important measures for research and care as well as their audit.

Study planning should include HCPs and providers as database holders, with data use, consent and privacy as important aspects for agreement and ethics approval. Early feasibility can determine logistics and speed of recruitment, and the need to engage a wide network of patients and investigators based upon disease prevalence. Utilising integrated hospital and primary care data should allow a network of investigators operating as a 'hub and spoke' to increase patient participation and retention.

Phase III employs adaptive design, stratification and comparator flexibility

Central coordination of a geographic investigator network can maximise patient retention, minimise patient impact and broaden investigator and patient involvement in research. The objective should be for high-quality, centrally coordinated research with a minimal burden over and above normal care for patients and primary care network co-investigators. In England, the remit of AHSNs may allow the building and utilisation of a research database infrastructure as a coordinating node for their geographic network with NIHR CRNs. Linking their data to those of CPRD and care.data for research and healthcare utilisation is closely aligned to their objectives. While studies are real world studies conducted with databases, these are not simple observational studies. Standardised assessments and laboratory sampling for safety, efficacy and stratification are all required. Nevertheless utilisation of a network of investigators, facilitating their participation through technology use will streamline study conduct, time and cost.

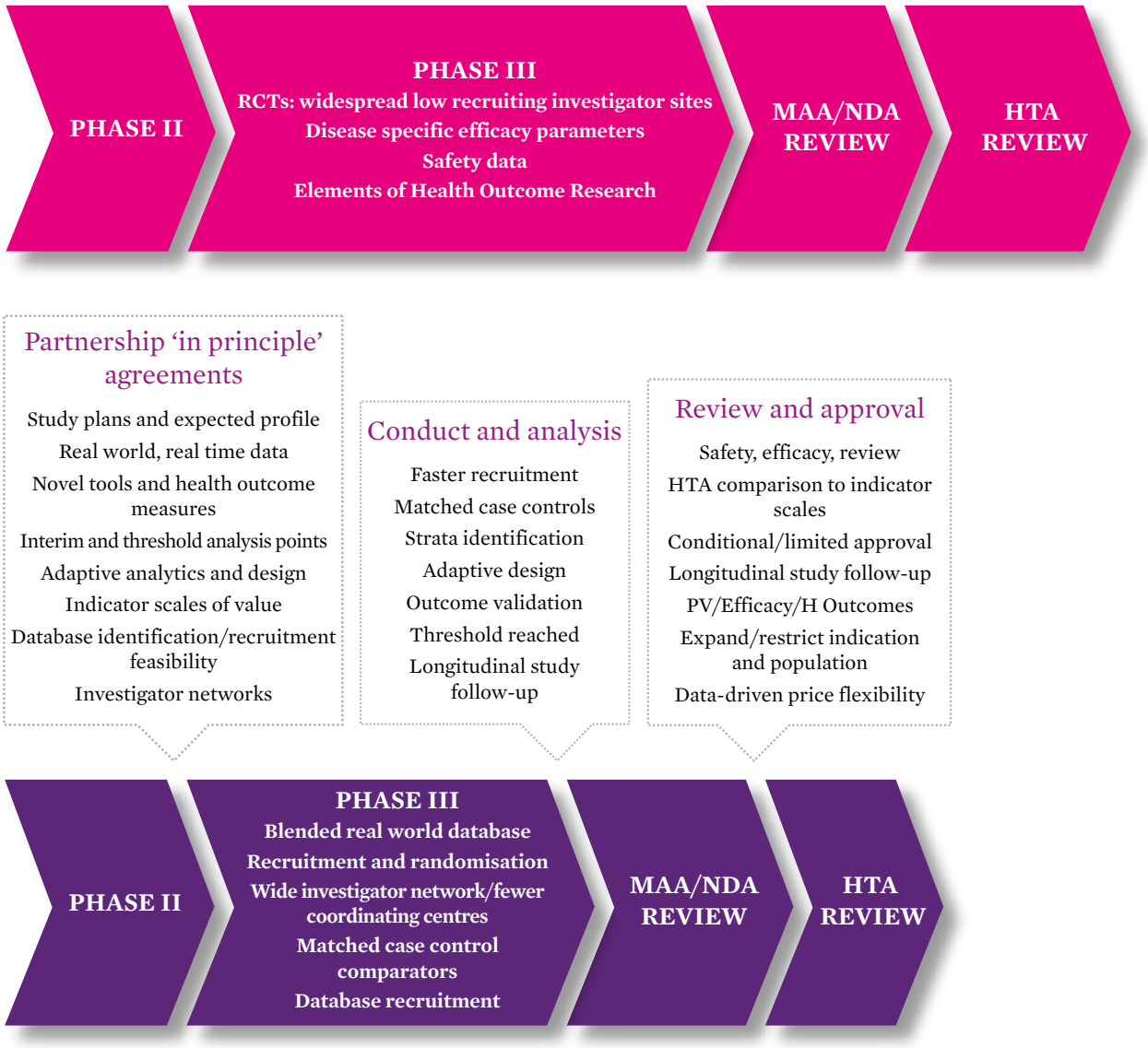
With database utilisation, novel 'big data' analytics begin to show benefit. Multiple associative comparisons, hypothesis formation and testing can be conducted in real time. Employing systems such as IBM Watson for trend and decision analysis as well as adaptive designs enhances the potential of databases. Adopting a Bayesian approach can allow both prospective and retrospective stratification through adaptive analyses during study conduct. These real time analytics can determine if the pre-agreed safety, efficacy or value thresholds have been met, and if so, a determination can be made to terminate the study for efficacy and file for approval early. Equally important, termination for futility can occur, based on safety or lack of value. In both cases, although further follow-up would be needed, the time and cost will be reduced compared to a traditional RCT. Even if the study runs its course, recruitment speed and improved investigator productivity reduce time and fixed costs of traditional studies.

Once the study has reached its threshold, assuming that filing for approval occurs, the development programme should continue during and beyond regulatory review to provide long-term data for further reassurance that early findings are confirmed. This mindset of continuous post-approval evaluation also permits simultaneous assessment of real world cost-effectiveness continuously generated within pivotal studies.

Real world data continuum enables regulatory and payer flexibility

If earlier filing occurs, it is possible that traditional regulatory approval requirements may not have been met. The agreements in principle may cover this eventuality. Study continuation, however, allows further data collection, which can be reflected in ongoing labelling, registries and restrictions in use. These activities can fulfil ongoing requirements to provide sufficient data for PASS/PAES assessments and should be integrated early into the development process and agreements. As such, medicines can be made available earlier but with phased approval and more controlled use. With continuous monitoring and assessment, and stratification as needed, maximisation of the benefit : risk ratio and cost-effectiveness is possible in an ongoing manner.

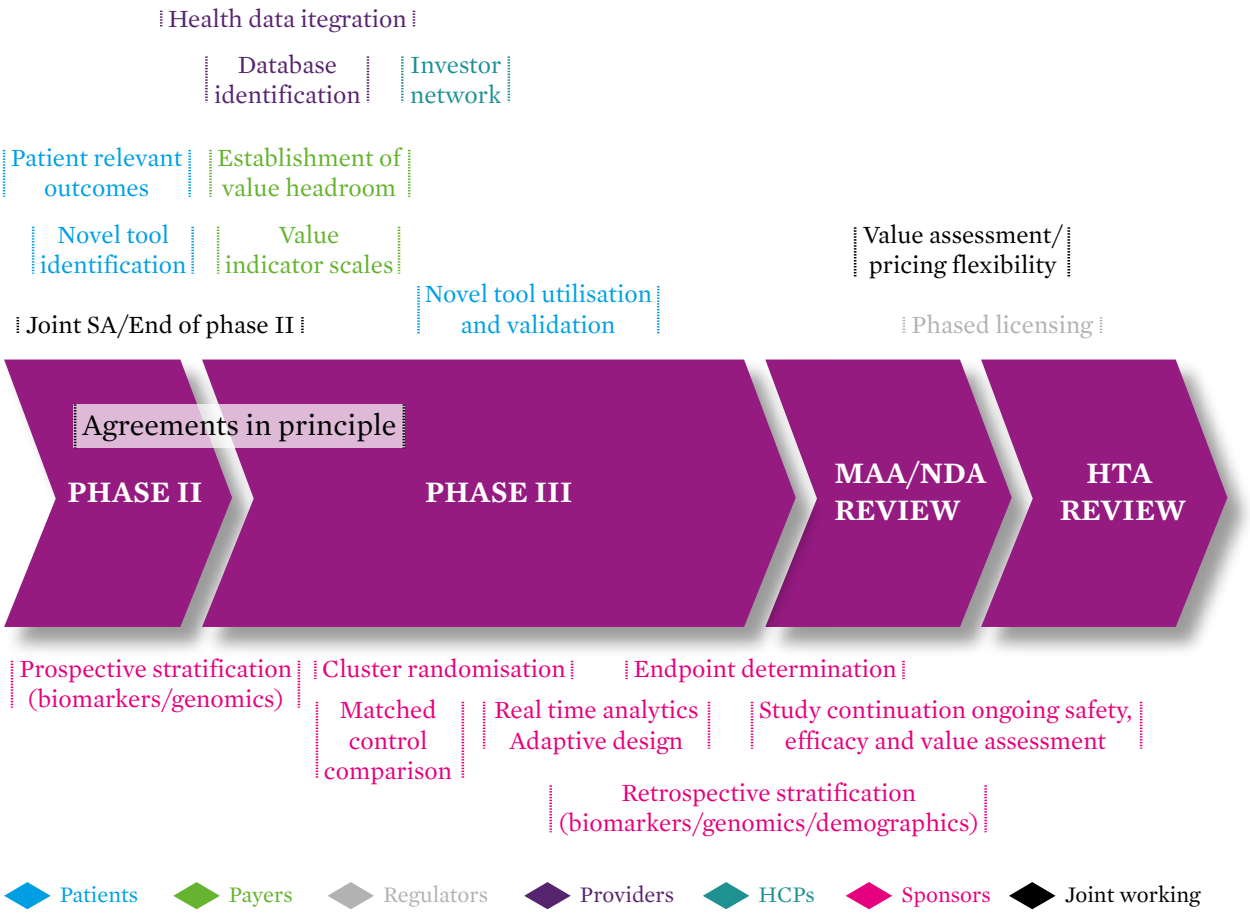
Figure 1: Reengineering medicine development interventions



Once analyses are formalised, MAA/NDA approval can be sought. If there was alignment with the principle of the pre-agreements, shorter review timelines might be possible. Similarly, applying data to the pre-agreed value indicator scales can assist effectiveness determination, and further discussion with payers for value, price and impact of uptake. Once formal approval is granted, a streamlined review of appropriate use and adoption within the healthcare system can begin, based on agreed cost-effectiveness. If limited incremental benefit is demonstrated, the value of the medicine will be commensurately lower. It may be that a sub-population or non-responder group is identified that improves cost-effectiveness and value. If so, this can be priced to reflect the benefit gained, and its use restricted to that patient group as appropriate.

As discussed above, studies would continue after approval to generate further evidence or validate surrogate endpoints. Further indications may also be planned with similar study designs to augment the medicine's use. In both cases, new data can be applied to continually assess the value and cost-effectiveness of the medicine, allowing price flexibility to reflect this. These data should also form part of the ongoing vigilance for new medicines and align with existing PSUR requirements. As data collection continues, if a medicine does not show sufficient long-term benefit, or new safety risks emerge, it will also be possible to reduce the price or withdraw the medicine.

Figure 2: Intervention points



Novel partnerships have global application and impact

Many innovators focus their development planning on major markets such as the USA, and secondarily on Europe or other regions. There will be a desire by companies not to compromise or duplicate their global plans. As such, global development requirements will need to be taken into account. If, however, a robust and scientifically valid plan exists, the strength of the data being generated should be the basis of an agreement to define approval requirements and what (if any) traditional Phase III RCT approaches are still required. Existing regulatory initiatives already discussed provide some hope that new approaches may be considered and harmonised in a variety of countries.

For those countries participating in the programme, agreement to the principles of the study parameters and value indicator scales is vital. Countries not participating should be made aware of the objectives to determine their likely regulatory responses. Some specific country requirements for participation in studies are likely to remain, but the database approach may be applicable in entirety to satisfy these, or be used in combination with a complementary but streamlined Phase III RCT.

With broad geographic uptake, a reduction in R&D costs and time would reduce pressure on high-risk investments. Early incorporation of effectiveness measures should encourage companies to prioritise more innovative projects, and investigate stratified approaches to derive greater patient benefit and value. With lower investment risk and the resulting portfolio efficiency, this should permit a greater degree of price flexibility to achieve a return. Additionally, in a stratified population where targeting augments efficacy and reduces safety liabilities, the volume and ineffective use of a medicine may reduce, but its unit price, value and affordability may increase.

Enablers, features and benefits

The enablers provide a platform for stakeholder behaviour change and leadership, to develop a partnership approach and thus greater predictability in medicines development.

Enablers

- Early engagement
- Patient involvement
- Electronic health record
- Database utilisation
- Novel analytics
- Distributed investigator networks

Features

- Agreements in principle
- Value indicator scales
- Blended/randomised real world study
- Matched control comparison
- Real time analysis
- Reduces investigator numbers
- Adaptive designs
- Stratification

Benefits

- Reduces cost and time
- Less complex IMP
- Speed of recruitment
- Speed of analysis
- Fail fast or file fast
- Relevant data for HTA
- Continuum of study assessment and phased licensing
- Evidence-driven flexible licence, value and price

Application

As with Adaptive Pathways and Breakthrough designation it is expected that the initial focus of such an approach will be on diseases of most urgent need. This should not exclude its applicability to other indications where there may be less urgency at an individual level, but with a major public health impact. Metabolic diseases such as type 2 diabetes and its causes, as well as dementia and other degenerative diseases, have a prolonged course but an enormous societal cost. This approach should be considered in such prevalent conditions for this reason.

Stakeholders

The main stakeholders under consideration are patients, providers, healthcare practitioners, industry/academic innovators, HTA bodies, payers and regulators. While all are currently involved and interdependent, their interactions are predominantly transactional rather than partnered. This is not surprising, as all have different perspectives and expectations emanating from these complex relationships. These involve regulating, purchasing and providing. As such, these relationships, together with a degree of suspicion, contrive to increase development complexity and slow the use and uptake of new medicines.

This proposal for real world, adaptive, database-led, matched case control designs capitalises upon current practices and opportunities, but develops them further to seek a robust, cost-effective approach. The proposal is deliberately provocative. The immediate stakeholder reaction is expected to state reasons why it will not work.

Nevertheless, ambitious leadership from all stakeholders to establish shared objectives can drive fundamental change to make this become reality.

A possible approach could be for stakeholders to agree to build on a premise to reduce the cost and time of medicines development, while increasing its relevance to facilitate cost-effective uptake. If such an objective could be agreed, the delivery of a proposal to achieve this should follow. Enabling earlier determination of efficacy, safety and cost-effectiveness through ongoing data collection, to adaptively manage licensing and value calculations, is a starting point. Once a methodology is agreed, it can be trialled and reviewed, and its further improvement determined.

Stakeholders will inevitably have their own perspective about what works well and what does not in medicines development. Additionally, there will be views about the positions of others. Developing external perspectives to understand what others may perceive as barriers could be helpful in achieving a greater degree of understanding and partnership. This does not mean that important regulatory principles should be compromised, but to gain success each stakeholder will need to recognise a benefit, and simultaneously relinquish or address an aspect of a real or perceived barrier. Some possible benefits and positions are discussed below.

Patients inform and influence research direction and its validity

There is public recognition of the need for research to be carried out in the NHS, with 89% willingness of respondents to participate, if a diagnosis is made.[33] A similar willingness is seen in patients with rare genetic diseases, even though there is an understanding that the rarity of their condition puts them at increased risk of being identified.[34] The UK's ability to access such a large integrated cohort would be world-leading and could be replicated elsewhere. Public concerns over trust and data privacy have, however, been raised in relation to care.data, reflecting the need for robust anonymisation or pseudonymisation.[35]

While there is great willingness for research participation, there is also great potential for patients and their representatives to inform research direction and priorities while directing aspects of development activity. Engaging patient representatives on study design can assist in determining not only QoL measures and value assessments, but also the overall impact and thus the worth of pursing a programme; while identification of novel tools and scales can validate new data collection measures for research and care. These can dramatically affect the sponsor, regulator and payer in understanding the value of the measures and the magnitude of patient impact, while reassuring patients of their relevance and reinforcing the importance of research and data protection.

Integrated provider databases within geographic networks enable real world studies

Providers manage infrastructure for healthcare delivery and to a lesser extent for research. They have a shared objective with payers for cost-effectiveness as well as resource and delivery planning. Resource utilisation for research may, however, be perceived as a drain on resource for healthcare. Highlighting the healthcare delivery

benefits of research through database utilisation may provide a different perspective. Additionally, analyses to audit cost-effectiveness of delivery would be further improved by an expansion of relevant patient data. Novel tools can further refine the relevance of such real world data, and seamlessly interface with routine health measures.

Utilising and enhancing databases would increase research efficiency, and reduce the time burden, as data collection could occur with relatively low additional effort. Simultaneously, interrogating databases for study recruitment could generate a revenue stream.

Integration of databases within the UK may be a challenge at this time; nevertheless, with NIHR CRN and CPRD as well-established infrastructures, with local initiatives, it is an area for AHSNs to lead on for a conjoint approach. Facilitating wider database utility with a research network would support HCP participation, as well as providing an effective infrastructure for audits of delivery and provider-led research. It would also allow management and ongoing monitoring of new medicine introduction.

Database-led networks enable more healthcare practitioners to actively engage

HCPs are the key interface with patients for healthcare delivery and as research investigators. The vast majority are not directly involved in research because of time constraints, lack of interest or bureaucracy related to GCP. It is expected, however, that HCPs will be interested in developing their practice and, with patients, wanting to be part of a 'learning healthcare system' that tests, develops and improves care.

With the expectation that 'every willing patient is a research patient' in the backbone of CPRD, devising opportunities for busy HCPs to participate in research in a time-effective manner is vital. This will expand the ability to utilise patient data in a real world setting and align with the patient approach above. Managing patient records within existing healthcare databases, and including relevant parameters collected through mobile health applications or devices could minimise the time for biometric data collection and expand study networks. Data collection in a real world setting provides much greater relevance to HCPs' clinical practice.

Developing a permissive research environment could realign the patient relationship from one predominantly based on paternalistic care, and expand the adoption and implementation of research findings into practice more quickly. This may be an additional incentive for research participation.

Increased research relevance and minimising time impacts may encourage greater involvement. Providing more routine background GCP training to HCPs would facilitate this, to enable development of a research mindset. It would also expand the research competence of an AHSN-led geographic network and promote more HCPs to undertake their own research projects.

Sponsor benefits from flexible study conduct should translate to pricing

Industry and academia are the main sponsors of medicines research. Sponsors aim to develop medicines to improve healthcare and provide sufficient return to investors. The high costs of development and impacts of delays in uptake, however, restrict reinvestment to assets that may have great benefit. These cost concerns lead to measures to reduce risk and, in larger companies, manage a portfolio of projects of varying risk and return. Smaller sponsors with no or limited revenue and perhaps only a single, significantly innovative project in development, see costs as a significant barrier.

In view of these substantial development costs and risks, many companies discuss expediting studies and 'failing fast', but are concerned that novel approaches may increase development risk. This perpetuates inertia in enacting change, despite widespread dissatisfaction with existing arrangements. Enabling a new mindset through successfully blending real world and traditional measures in a faster, lower-cost evaluation should provide development efficiency for companies of all sizes, because of partnership agreements quantifying and reducing risk.

Simultaneously, improving the quality of the effectiveness data generated in these studies should accelerate value assessments, and a better understanding of payer requirements and the impacts of price. Reduced costs and time will also increase affordability of development projects and thus portfolio efficiency. These benefits can be passed on as flexibility in pricing of medicines and improved cost-effectiveness.

HTA bodies and payers design indicator scales early to guide and measure value

Payers are increasingly concerned about rising healthcare costs, affordability and the efficient management of resources. Given the aging population, this is particularly concerning for degenerative diseases and cancer. Improving the quality of cost-effectiveness data and assessment by HTA bodies against prior agreements will allow payers to better understand projected impacts and benefits of an intervention, and thus the management of scarce resources. Early involvement in discussions will facilitate greater alignment, but also require resource provision for a greater number of early development projects that are more likely to fail.

Based on the projected health benefits of a medicine, HTA bodies can determine the 'headroom' for value that exists, and how price would influence cost-effectiveness. This can provide important insights to sponsors for their progression decisions, based on likely payer adoption. Although during development some aspects will change, an agreement in principle to the potential value should be possible. This will provide an assessment of the likelihood of achieving cost-effectiveness thresholds based upon the emerging profile, building in flexibility of pricing because of reduced development costs.

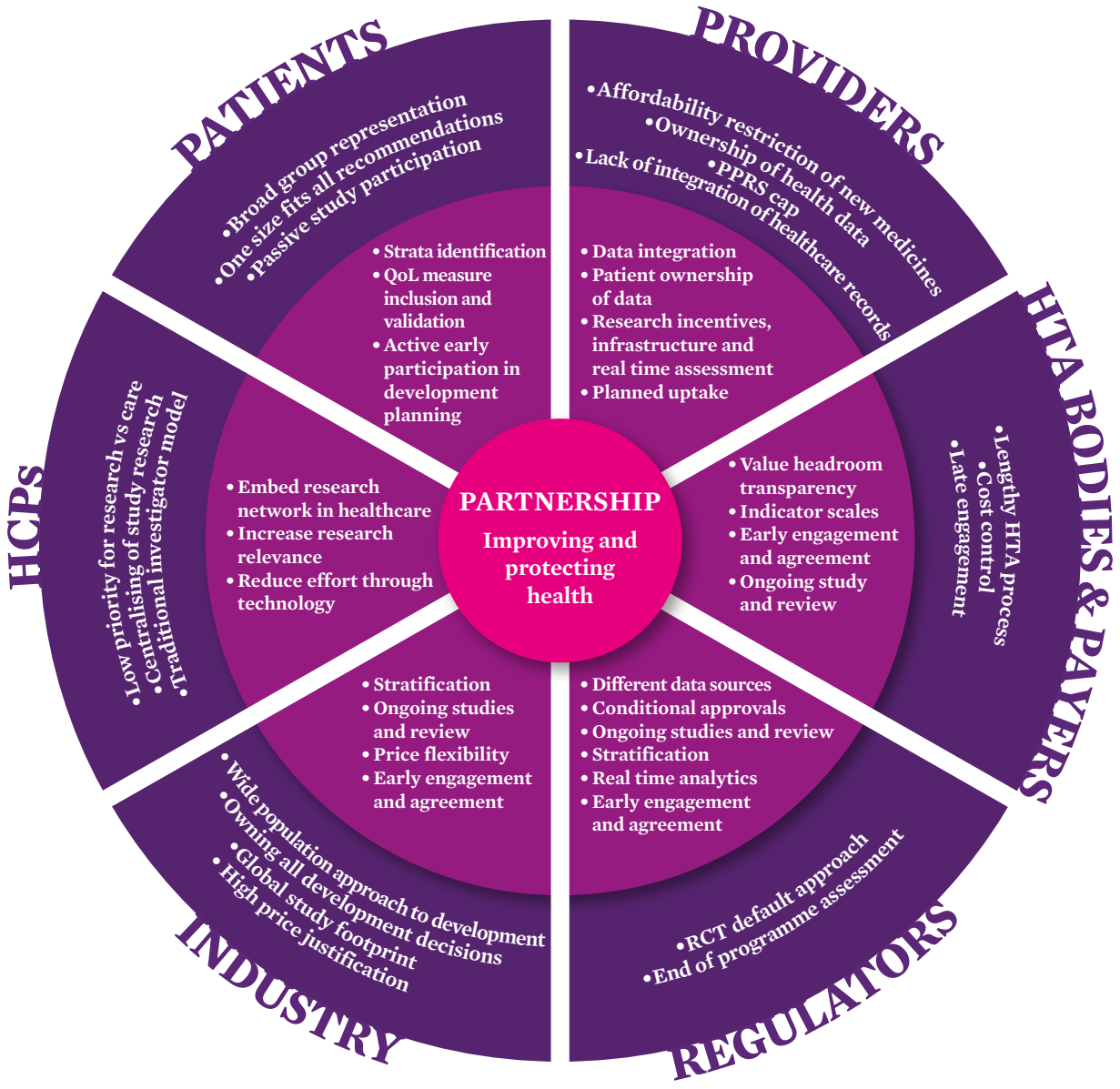
Regulatory authorities accept robust data generated through non-RCT methods

Regulatory authorities have approval criteria based upon minimum acceptable levels of efficacy and safety. These criteria should not be compromised, but different methods of data generation for approval should be considered. More adaptive review and approval to accelerate innovative medicine availability, or rapidly terminate futile studies, should also be incorporated. Agencies have been taken to task for scrutiny of new and existing medicines, with instances of 'safety scares' causing public concern. This has driven a more conservative approach to medicines licensing, based upon a drive to protect public health. This increases the development hurdles, time, cost and post-approval requirements. The lack of predictability of RCT data has already been discussed. As such, data sources more reflective of clinical practice may be helpful. Moving to greater use of real world data, reviewed in real time, would provide greater confidence in the profile of a medicine and could provide ongoing data provision for phased approval, stratification, controlled use and greater robustness of vigilance data.

Regardless of the source of the data, it will be important to ensure that all data are auditable to a standard equivalent to the quality of GCP. This will aid the development of an ICH-like standard for recognition of real world database studies conducted across multiple countries. This will enable wide adoption and substantial efficiencies to be realised.

Adopting new methods to deliver evidence standards does not set a precedent. It does, however, reinforce the integrity of the standard and demonstrate an adaptable approach based on the profile of each unique project. Neither does a partnership approach diminish the role of the regulator. Its role is enhanced as the arbiter who agrees the standard and determines the outcome, but is creative about solutions to facilitate the path.

Figure 3: Possible stakeholder changes to achieve shared objectives and increased partnership



Recommendations

It is recommended that a new model of development be urgently investigated to replace high-cost, high-risk Phase III studies that do not reflect clinical practice, with a blended real world, matched case control approach. Real world data incorporation should be driven by patient insight and needs, and captured through novel monitoring tools, to allow assessment of quality of life in parallel with regulatory assessments of efficacy and safety.

Construction of value indicator scales that identify the expected health value to be derived from the target product profile (incorporating efficacy, safety and quality of life measures) should be agreed in advance. These scales can be used as a reference for emerging data to define price points that will meet cost-effectiveness thresholds. Studies should preferentially be conducted using healthcare databases, with a network of investigators to rapidly identify and recruit patients, and be streamlined through cluster randomisation and matched case control comparisons. The UK can lead such approaches to set standards for use and establishment of other suitable databases globally.

Real time analyses that influence adaptive designs and stratification should be incorporated into programmes to allow early termination for futility, or early MAA/NDA filing. These decision points should be based upon achievement of pre-agreed thresholds, perhaps for surrogate measures. Licences should reflect the population studied, with clinical use restricted by labelling. The continuation of studies longitudinally can subsequently validate clinical outcomes and expand use while further studies can include new populations or indications to expand or restrict labelling based upon emerging data. The value proposition should similarly adapt and be reflected in price flexibility to ensure adequate reward for sustainable investment and innovation. The savings in development time and cost enable such price flexibility with improved cost-effectiveness and affordability to enable uptake of new medicines.

This is a substantial change in development, assessment, approval and use of medicines based upon process redesign. For this proposal to begin to become a reality, all stakeholders should look for opportunities to work in partnership for mutual benefit, and consider tangible actions to demonstrate their commitment to do so. Further, piloting projects through this process will demonstrate parties' commitment to partnership working and refinement of the approach through operational experience.

Conclusion

For all stakeholders, there are challenges in the changes proposed. Some of these may be legislative. If, however, there are shared objectives with an open approach towards commonality and trust, and agreements in principle, removing barriers should follow. This requires personal and organisational courage, as well as leadership. If needed, legislation can be amended to embed a different approach to developing and evaluating medicines that will deliver a substantial mutual benefit while improving public health.

There has been much discussion over new methods for medicines development, but only incremental activity. Given the length of the development process, transformative action cannot be postponed. While we cannot expect complete certainty, sharing objectives and working in partnership to develop radically new systems has to occur. Waiting until a perfect system is designed will take too long.

Potential Adaptive Pathway projects have already been identified. Further expanding the concept as discussed here, by piloting database utilisation for development projects, with agreements in principle and value indicator scales, will demonstrate willingness and adaptability to find solutions. Robustly determining utility, failing fast or filing fast to develop cost-effective medicines with increased pricing flexibility will benefit us all.

We invite stakeholders to review these proposals and develop them further, looking for common ground and enhanced partnership opportunities to benefit from and globalise a new process. This leadership behaviour can be the disruptive change needed to rapidly reengineer medicines development from the current adversarial system, which restricts translation of innovation and drives ever-increasing medicine prices, into a model fit for the 21st century.

Glossary

AHSN	Academic Health Science Network
CMC	Chemistry Manufacturing and Controls
CPRD	Clinical Practice Research Datalink
CRN	Clinical Research Network
EAMS	Early Access to Medicines Scheme
EHR4CR	Electronic Health Records For Clinical Research
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCP	Healthcare Practitioner
HSCIC	Health and Social Care Information Centre
HTA	Health Technology Appraisal
ICH	International Conference on Harmonisation
IMI	Innovative Medicines Initiative
IMP	Investigational Medicinal Product
MAA	Marketing Authorisation Application
MAPPs	Medicines Adaptive Pathways to Patients
MRC-NIHR	Medical Research Council – National Institute for Health Research
MHRA	Medicines and Healthcare products Regulatory Agency
NDA	New Drug Application
NEWDIGS	NEW Drug Development ParadIGmS
NIB	National Information Board
NIHR	National Institute for Health Research
NOCRI	NHS Office of Clinical Research Infrastructure
OLS	Office for Life Sciences
PAES	Post Approval Efficacy Study
PASS	Post Approval Safety Study
PIM	Promising Investigational Medicine
PSUR	Periodic Safety Update Report
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Controlled Trial

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