

Vermilion Life Sciences

Exploring new connections and alternative approaches



Bringing medicines to *life*

# Reengineering medicines development

Summary output of a stakeholder  
roundtable on cost-effective development  
of affordable innovative medicines

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## Introduction

ABPI and Vermilion Life Sciences held a stakeholder roundtable on 4 March 2015 to review proposals from *Reengineering medicines development*.<sup>1</sup> Multiple stakeholders including regulatory agencies, Health Technology Assessment (HTA) bodies, patient groups, clinicians, academia and pharmaceutical companies discussed challenges in affordability and duration of medicines development that lead to delays in access due to cost-effectiveness concerns, and ways to overcome these.

## Opening plenary discussion

While the focus of the meeting was the UK, it was recognised that the UK, as part of Europe is a key player in global development. It was acknowledged that the UK allows wide stakeholder engagement to facilitate development of a new approach and subsequently broaden it more widely, even though no single country could change the model alone. Reimbursement was recognised as being a predominantly European driver, although US awareness via the Affordable Care Act and Personalised Medicine initiatives is growing. Globally expanding new thinking through identification of shared interests, to advocate jointly upon them was recommended.

Technology is beginning to enable new development concepts, but novel approaches have not been pursued consistently because of conservatism and risk averse behaviour. This leads to maintaining existing paths based predominantly upon regulatory approval endpoints. Industry has maintained a conservative model but, given pricing and reimbursement challenges, recognises an increasing unsustainability. Industry is, however, concerned about increasing regulatory risk so there is a reticence to be a first mover, even if there are benefits from doing so. It was agreed that benefits to streamlining data collection and its relevance exist, and could be delivered through healthcare database real world data collection. However, the lack of integrated healthcare IT systems was noted as a barrier needing attention.

Stakeholders having greater mutual understanding was seen as a major enabler. To build stakeholder partnerships, trust was identified as a critical success factor to enable joint working and cross-fertilisation of ideas. It was queried why patient views were not engaged earlier. Despite recent improvements, it was felt that greater patient partnership would produce better solutions and improve research direction. It was noted that engaging patients early could lead to hard decisions on medicines provision later if accumulating evidence did not support use of a new intervention, even if there may be some individual benefit. Involving patients early in discussions would help transparency about choices and trade offs.

The positive intent of Medicine Adaptive Pathways to Patients (MAPPs) and the Early Access to Medicines Scheme (EAMS) was recognised. Including enablers, such as real world data, stratified medicine and the 100,000 genome project, had potential to further increase speed, relevance and personalisation of development. Establishing shared strategic intent based on these approaches could increase stakeholder understanding and transparency, leading to new methodologies that still maintained existing approval standards.

Studies such as I-SPY and SIGNATURE have shown that adaptive designs outside of Randomised Controlled Trials (RCTs) have validity and can increase flexibility and relevance. Regulatory agencies and HTA bodies are receptive, which may lead to wider global adoption. It was agreed that modelling value through use of Value Indicator Scales or similar techniques, may better predict and model the value of expected efficacy and safety profiles, but include patient, family and carer benefits to guide important quality of life measurements. Establishing a new process to pilot some projects as pathfinders, for further refinement, was concluded as being desirable.

<sup>1</sup>*Reengineering medicines development*. Available via ABPI: <http://www.abpi.org.uk/media-centre/newsreleases/2015/Pages/050315.aspx> and Vermilion Life Sciences: <http://www.vermilion-lifesciences.co.uk/stakeholder-roundtable.html>

## Roundtable breakout summaries

### Data for regulatory submission

Real World Data (RWD) has great potential as a data source, but needs better implementation in clinical trials, rather than solely in observational post-authorisation studies. RCTs' very rigid infrastructure is complex and costly, thus RWD needed to remain close to the patient experience. Simplicity of collection was advocated, whilst improving robustness of the data.

Improving robustness through research skills training, to increase understanding of how data are used for healthcare would be an opportunity. Bodies such as TransCelerate may be able to assist with standardising training to improve data quality.

Regulators are keen to simplify development, are prepared to accept RWD, and actively encourage companies to engage in early dialogue. The 'noise' in RWD can, however, reduce safety and efficacy 'signal to noise ratio' making decisions more difficult, even though it better reflects clinical reality. Companies have been reluctant to engage early, perhaps because of concerns that engagement will increase regulatory hurdles. Greater global regulatory alignment is required to reconcile 'noisy' RWD but could permit limited initial regulatory approval with ongoing follow-up to expand the label.

Studies that require complex prognostic and predictive biomarkers do not lend themselves to pure RWD approaches, but even these trials can be made simpler, more relevant and efficient. A mix of traditional and RWD approaches would be beneficial. A challenge for implementation of RWD is that the infrastructure (including Clinical Trial Authorisation (CTA) and ethics review) is set up for RCTs. This creates hurdles and barriers to RWD approaches.

A test case, to demonstrate the benefits, could move this from concept to reality. A promising lead that cannot easily be developed through normal routes could be examined to determine the speed and cost benefits of RWD and stratification.

### HTA prediction of value

Greater use of joint scientific advice would assist earlier decisions and increase validation of new approaches. Modelling of value is a challenge as future predictions are made through the lens of decisions based on today's practices. Having a greater weighting of the influence of value on investment decisions, would enable better exploration of uncertainty and may assist new approaches for adaptive licences. Payers are flexible in accepting data and are not limited to one methodology, but the issue of cost-effectiveness and affordability remains. Different payers have different levels of flexibility, so there is a lack of standardisation.

Will stratification lead to a higher price based on the willingness to pay for 'different' Quality-Adjusted Life-Year (QALY) by disease area? Is cost per QALY sensitive to pick up benefits in all diseases? Is there a need to link willingness to pay with differential thresholds for different diseases?

Cancer development is the closest to a new approach at the moment and is pushing the boundaries. If we can solve this for cancer it may help solve it for other areas, particularly for chronic diseases where costs will be significant. Nevertheless we need to recognise that funding for medicines is limited. Gaining input at an early stage may assist in changing the approach to flex price and volume with differential pricing across different indications.

Engaging patients earlier may allow better decision making when there is a greater degree of uncertainty, and assist in further evidence generation requirements. It can also assist in discussing a potential exit strategy if one is needed.

## Collaborative environment to support research

Where collaboration has worked well, a framework discussion to agree the objective was put in place with an open transparent approach and a shared agenda to look for solutions and new ideas. Although the New Drug Development Paradigms (NEWDIGS) programme discussions were complex and detailed, they were very valuable with a high level of trust. A theoretical approach was made tangible because of the focus on realising the benefit to patients in a project.

Trust and partnership takes time to establish through behaviours, words and actions. A high level of engagement, and a high degree of listening is required. Having patient outcomes as a focus helps, as does being prepared to stand in each other's shoes to understand better. The behavioural importance should not be underestimated.

Sharing information on objectives and areas for working together is key to partnership. There needs to be a safe place to share thoughts and reduce adversarial positions. Adaptive Pathways is starting this, but has no discussion on price or value input during development. Incorporating Value Indicator Scales would help, as this would provide a tangible focus on how best to manage design and progression of studies, and provide a weighted measure of value for investment decisions.

Company investment decisions currently examine benefit risk and value (price) that can be achieved. If this can be discussed early to clarify success factors, value concepts and flexible pricing can be better integrated into planning and, if needed, back-loaded into financial projections based on when high value evidence is expected. However, QALY is not a very sensitive tool to generate price points, so refinement of measures to estimate value may be needed.

Clarity from regulators (and HTA) about how a new process might work may help, but it was recognised that it is not the regulator's role to design development programmes, whereas they will respond to what is presented to them. As such, sponsors will often be conservative, based on their preconceptions of regulatory expectations, when in reality regulators may be more flexible. Shared openness to new ideas may be an enabler to break ever-escalating cycles.

Affordability has become a more prominent concern recently because of Hepatitis C products, which are cost-effective, but high cost. This is also the case with some oncology products and is of increasing concern to payers overall. Improving development time may have a substantial impact on price flexibility. Can time be improved because of faster, database-led recruitment with (in some cases) fewer patients? Can new analyses clarify benefit/risk profiles sooner to accelerate decision points?

If phased approval can occur, more open discussions and agreement to price flexibility can increase transparency of expectations. Currently the expectation is that price will only fall after launch. While it may fall, it should have the ability to rise and reflect the level and value of the evidence. The fundamental economics of affordability need to be recognised, however.

Engaging with healthcare professionals (HCPs) as gatekeepers of data, to motivate them as active participants in research, can be difficult. Helping them understand how RWD can benefit them and their patients' care is important to improve the mind-set of research as part of care.

## How patients can better influence clinical research

The nature of clinical trial data does not always address important patient relevant aspects. It is important not to focus on easily measurable, but less relevant, areas. A bigger impact can be made with patients by talking about really difficult areas. A citizens' jury on benefit/risk may be helpful to better understand risks that patients feel are worth taking, to achieve a beneficial outcome of value. Discussions should include [the impact on] carers and children. The management of risks and benefits for children are most difficult.

Often patient interactions are transactional rather than partnered. Early patient input can inform decisions, design, study operations and reporting tools. There is a major opportunity to involve patients but the pathway is not clear. Care is required, but Codes of Practice are not a barrier for partnership on development projects, but they may need to be reviewed to decide how best to engage proactively with patients. Leadership is important to ensure appropriate guidance, process and consistency. This is easier in rare diseases with a small patient group, and may serve as a model for stratified medicine in larger populations.

Building early dialogue on existing relationships may help. Patients like talking to other patients, so involving patients in trial design may be a better approach to manage objectives and logistics of participation, to minimise patient burden and increase study retention. Having awareness of projects on a website or through other activities may be of use. Best practice on what is working well in trials from a patient perspective can be shared more widely.

It is recognised that trials have increased in size with procedures for collection of data that are inconvenient for patients and impact their recruitment and retention. For example, an ulcerative colitis trial without colonoscopy had vastly improved recruitment. Involving patients and regulators in these discussions early was recognised as being important.

Leverage for engagement are to create a research-aware culture in the National Health Service (NHS) that supports the willingness of patients to participate, and recognises research as an essential part of a clinician's patient engagement and delivery of high quality clinical care.

Blockages to implementation of research within providers should be identified and addressed. Business managers were cited as potential blocks if they do not appreciate the importance of research to improving and delivering care targets.

Using web-based tools and other communication vehicles to link local and secondary/tertiary healthcare systems in a vertical manner would help both care and research.

## Integrated health data

There is a lack of clear understanding of what data are available and how to access data for what purposes. As such, a simplification of entry points is needed, with a single access point with consistent governance. This would reduce cost of entry and provide a focus for inward investment, to allow greater access to and use of data. Access to Clinical Practice Research Datalink (CPRD) services is recognised as a strong platform dataset with a single point of entry.

Data quality was acknowledged as an issue, with low quality of primary care data limiting utility. There is a data bias depending on what is captured, so guidance on more consistent understanding of important parameters is required. The ability to adapt trial design will be dependent on data quality, and its real time availability. Promoting case studies of integrated healthcare and research, e.g. TransCelerate & Salford Lung Study to facilitate replication of vertically integrated health systems, can enhance better practice. This would allow better medicines optimisation by aligning data to follow the patient's journey rather than having data aligned to the provider organisations. It could then set a better baseline standard of care for future development projects. Local vertical integration may lead to competition between sites with different standards. This may prevent national integration, so common data standards are needed (outside the UK also). CPRD is building a platform to get primary care data on a daily basis, which will increase real time utility.

There is a need for a plan to integrate health data and improve its quality. This may be linked to determining ownership and decisions on access. There is a lack of clear responsibility at data entry level, and perhaps a lack of understanding of the importance and value of the data. A collaborative forum may be useful to assist in delivering better integrated health data.

Public-private partnerships may be the way forward to build integrated data platforms with good quality data, but clear data responsibilities and governance are needed.

## Additional commentary from invited stakeholders

**RWD** is not solely used in observational studies. It can be utilised for RCTs, simplifying data collection and integrating daily practice into research. RWD can be challenging due to confounding, but there are opportunities for RWD in pragmatic trials. The act of randomisation and blinding in RCTs introduces bias through an artificial clinical situation that changes patient and HCP behaviour. Conversely, running an unblinded study introduces bias through lack of control. The RCT placebo group is thus not reflective of ‘no intervention’. Blinding is possible in RWD and with cluster randomisation. Single, double or observer blinding strengthens pragmatic studies, retaining the Investigational Medicinal Product simplification that is not possible in blinded RCTs. Flexibility is needed, dependent upon the objectivity of the end points, but even single blinding may not be suitable with subjective end points.

The totality of the evidence base should be considered. An approach whereby Phase II RCTs establish biological proof of concept, permitting further pragmatic/RWD studies in Phase III, can allow a similar population to Phase II to be studied but with more clinical relevance. This enriches the data, but avoids the dilution of effect sometimes seen in Phase III through broadening study populations. It may also better define the patients who benefit (perhaps defined by biomarkers) for initial approval, which may be expanded sequentially over time.

On **Good Clinical Practice (GCP)**, while the overall aim of GCP is clear, it can be costly and inefficient as a singular approach. GCP prevents pragmatic trials being pragmatic. In addition, GCP is interpreted differently by individual sponsors, leading to inefficiency for investigators working with multiple sponsors. A more standardised approach across sponsors (perhaps facilitated by a body such as TransCelerate) or with a master protocol and Case Report Forms would simplify designs and operations.

**Ethics and governance** of data use require further reflection on the frameworks to support the presumed ‘public interest’. Alignment of public, healthcare and sponsor interests in data use cannot be assumed, and an inclusive, ongoing process, with a wide-ranging open ethics debate should take place. The ability to change preferences and needs over time should be incorporated. Data use governance expands beyond patients, to include family and carers, members of the public and future patients. A wide public discussion should consider potentially broader implications for the structuring of healthcare and research.

Anonymisation and pseudonymisation should not necessarily be relied upon. Ensuring appropriate governance of data use, including mechanisms for respecting the extent of consent over time is of great importance. To this end, the concept of ‘data ownership’ is not helpful in devising ethically appropriate data governance, but the concept of use and ongoing consent may be of more relevance. While broad consent may be appropriate in some cases, this is only so in the circumstances of well-governed research and in relation to applicable norms of privacy and disclosure. Additionally, patient ‘ownership’ of data questions whether patients, and the public more generally, would be able to profit from ‘their’ data financially.

## Conclusion

The roundtable and other feedback reflected on future partnership opportunities to improve the time and cost of development and its relevance to clinical practice. Delays to uptake and costs of new medicines were seen as important interlinked areas that could act as a focus for shared objectives from new processes. These reflections can form a platform for next steps, to investigate tangible stakeholder actions as suggested below, building on these proposals with identification of pathfinder projects acting as pilots to test new approaches.

# Reengineering medicines development – stakeholder output

## Proposed actions for a UK-based approach, for further consideration of expansion to common standards in Europe and beyond

Patients	Providers	HCPs	Industry	Regulators	Payers / HTA
Build understanding of medicines development and communication of how they can shape it	Develop objectives to incentivise research as a priority that augments care	Build greater cross-sector experience to better understand needs and objectives. Enhance partnerships with academia and public-private partnerships to identify pilot projects, their funding and concept testing through real world studies.		Increase communication of receptivity to discussion and new approaches, through proactive responses to advice and interactions and how it fits with existing regulatory guidance	
Drive agenda for research direction and study simplification based on directional desires and needs	Facilitate infrastructure and new roles to embed research as part of care	Support need for research and its training to be a part of integrated care with relevant career options	Jointly develop methodology to enhance design of real world data approaches that streamlines study conduct and operations, flexibly addresses bias and has utility for adaptive studies and licensing based on sequential expansion of populations and evidence base. Seek pathfinder projects as pilots		Early engagement to provide predictive value scales for sponsors to allow tailoring and stratification of development plans
Include carers' and children's perspectives as well as increasing public consideration of data use, governance, ongoing consent and 'ownership'	Integrate data and its quality as part of routine record keeping, and design governance oversight with patients to include security and interoperability	Increase audit of care to improve quality and consistency of data capture	Include patients and their needs and account for this in plans to build into value assessment for decision gates	Develop pathways for flexible approval that support continued research and stratified/phased licensing and expansion	Develop pathways for flexible review of ongoing data generation to assess value in stratified and phased adoption of use
Consider patient-to-patient communication forums for trial participation	Engage in open public debate regarding data access, ownership, governance, use and consent permissions		Access regulatory and HTA opinions early, to build flexibility for adaptive decision making, stratification use and price		Investigate refined measure of value beyond the QALY. Consider differential disease thresholds or tools to inform QALY measure

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