



Kinapse White Paper

Real World Development: Increasing Value for Patients

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Real World Development: Increasing Value for Patients

Kinapse Consulting, 2009



The traditional drug development paradigm must change. We propose a fundamentally new approach which will create a win-win partnership between industry, academia, health authorities, health technology assessment (HTA)/health economic program (HEP) bodies and patients. We call this new approach “*Real World Development*” the underlying principle of which is to constantly assess the product in as close to post-marketing use as possible. Key components of Real World Development are the use of adaptive trial design and capitalisation of existing real world data sources. It enhances the evaluation of benefit/risk, enable earlier patient access to innovative medicines, and improve value for money. We have worked with a range of industry stakeholders to craft this approach. To make progress, stakeholders need to further understand the benefits of the approach and work through how to apply it to current development programmes. We have therefore built a detailed financial model to support the design and funding of a Real World Development programme, as well as to support decision-making on the most appropriate programmes with which to pilot the Real World Development approach.

Drug development today is unsustainable

The drug development model has remained relatively unchanged for the past two decades, following a well-trodden path of target and compound identification, assessment of efficacy and toxicity in animal models, extensive clinical trials in humans, submission filing, approval and launch with continuing post-marketing vigilance activities (Figure 1).

Phase III pivotal trials, which carry by far the largest costs in drug development, are designed to demonstrate the clinical effectiveness of the drug at the selected dose, and also to gather as much evidence as possible to demonstrate ‘safety’ (i.e. an acceptable benefit/risk profile) in exposed patients. Phase III trials, by their nature, take place in a very tightly controlled environment and tend to involve sizeable patient populations just prior to the finalisation of the dossier for regulatory approval.

Regulatory approval for the drug’s launch is premised on an independent, expert assessment of the drug’s quality, efficacy and safety. Naturally, this ‘go/no-go’ decision is typically made when as large a body of evidence as possible has been gathered. High profile post-launch drug withdrawals resulting from safety concerns have had a negative impact on the reputation of both the pharmaceutical industry and its regulators. This has encouraged the regulators towards a more conservative, risk-averse stance to approval.

Securing HTA/HEP support is also critical to establish the economic viability of a new drug. This also takes place very late in the development cycle (after Regulatory filing and/or approval). At this point, if the product is not granted reimbursement

the pharmaceutical company must decide whether there is an evidence base to support further studies and re-submission of the HTA/HEP dossier.

Patients can usually be prescribed the product only when the key safety, efficacy and value questions have been answered. Truly innovative medicines generally take many years, and sometimes two or more approval cycles to reach this stage. Thereafter, physicians prescribe the drug based on the available product information, but typically without further controls or requirements for monitoring performance of the drug other than submission of spontaneous adverse event reports.

As it takes longer to bring new drugs to market, the period of marketing exclusivity decreases, further diminishing commercial return on new medicines and tending to drive increasing prices of patented products, which in many cases are not affordable as a result.

This situation is unsustainable. The future of the innovative pharmaceutical industry is genuinely under threat. As a result, the interests of patients with serious unmet medical needs will be under-served. The industry and its regulators, with the full support of governments, need to proactively start the process of change now.

Changing development for the real world

The Real World Development approach which we propose (Figure 2) bridges the translational research gap (characterised in the UK by Sir David Cooksey) between clinical trials and the establishment of the drug in general use.

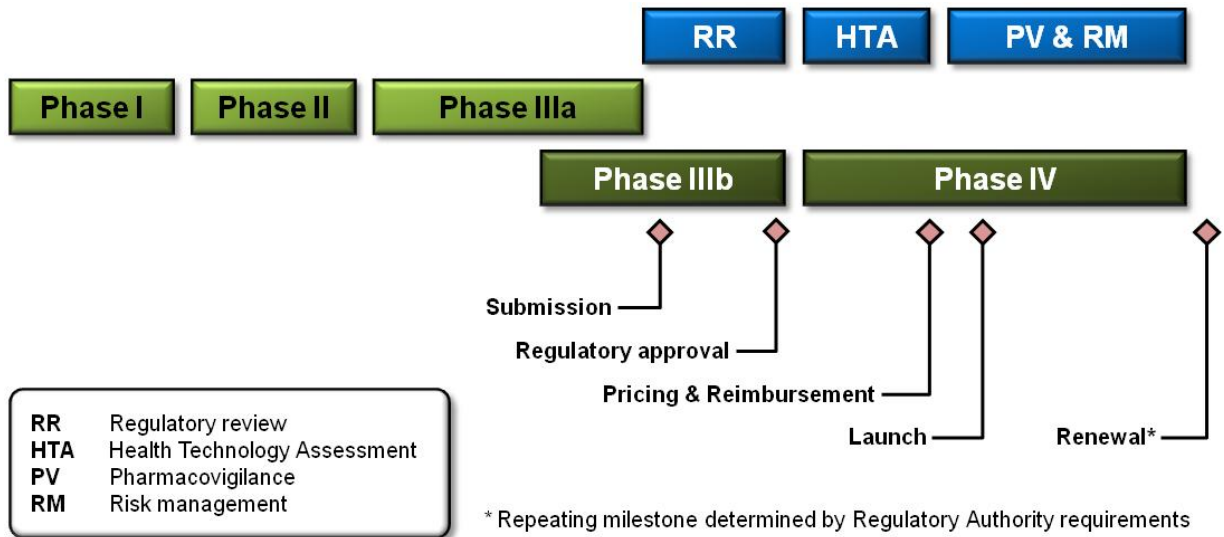


Figure 1: Traditional Development model

The goal of this new approach is to profile the clinical benefit and economic value of innovative medicines in carefully monitored ‘real world’ settings. Our approach acknowledges that new drugs must be shown to bring benefit to patients in a real world setting, a context that tightly controlled Phase III clinical trials cannot emulate.

Development approach is defined such that confidence of clinical efficacy (CoCE) can be demonstrated from a lean Phase IIIa double-blind randomised clinical trial, sized solely for demonstration of efficacy, while supplementary trials are carried out in parallel to establish the product’s real world value for specific patient populations in respect of its clinical efficacy, safety, risk-benefit (Confidence of Benefit, CoB) and economic value (Confidence of Value, CoV).

The underlying principle of our approach is to continuously assess the product in as close to post-marketing use as possible. The Real World

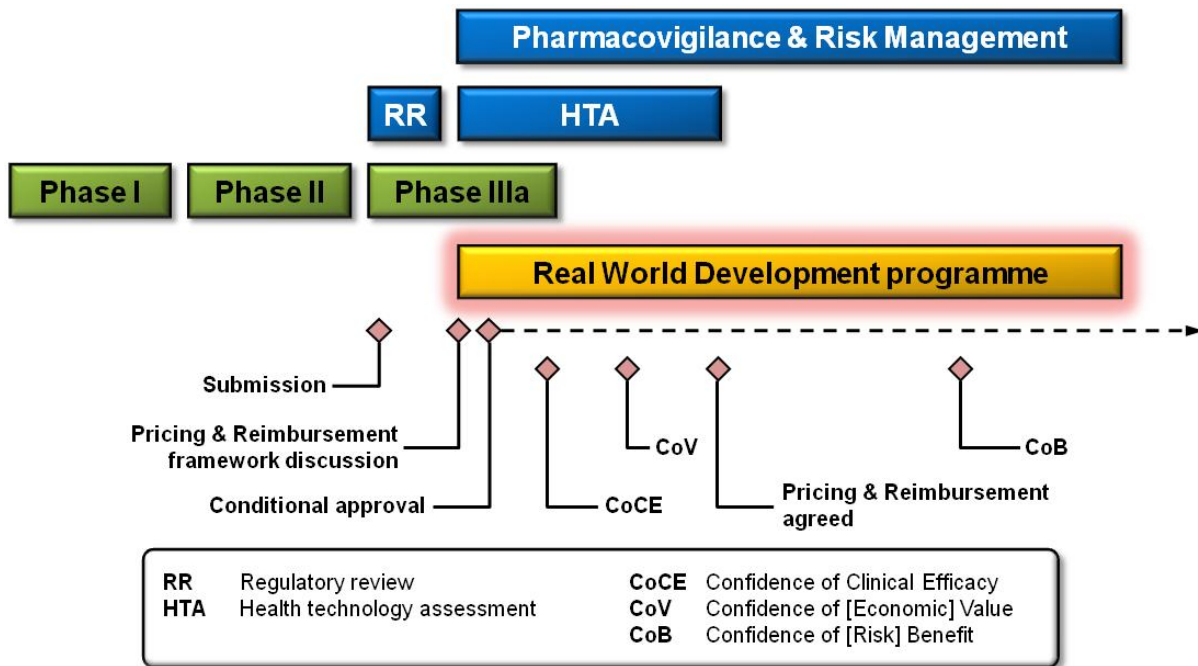


Figure 2: “Real World Development” model

The main features of the Real World Development approach include:

- A patient-focused approach allowing earlier access to innovative products to controlled groups of patients
- An understanding of how the drug works in a real-world setting, improving confidence of clinical efficacy and risk/benefit
- Earlier and better characterisation of risks allowing for more rapid and effective drug development decisions actively engaging patients and other key stakeholders
- Parallel processing and evolutionary trial design that accommodate adaptations based on the emerging 'in-stream' clinical data set
- Capitalising on various existing real-world data sources, including observational data sets and electronic medical records
- Eliminating the need for traditional hypothesis-testing clinical trials in Phase IIIb and/or IV.

Critically, we believe the Real World Development approach strengthens patient safety through ongoing monitoring of exposed patients throughout

the duration of the programme. Also, standards for patient eligibility and consent are maintained throughout the programme, with reassessment of eligibility criteria as the data set expands.

Drugs most suited for the Real World Development approach include those for the treatment of indications and conditions where patient populations are discrete or limited. These include orphan drugs, end-of-life drugs, treatments for rare cancers, and for situations of exceptionally high unmet medical need. Real World Development allows them to be investigated in a commercially and clinically risk-contained environment.

Ultimately we expect the approach to support earlier decision-making based on near real-time information in the interests of public health. These decisions require a shared understanding of the approach by the sponsor and other major stakeholders including payors, regulatory authorities, HTAs, patient advocacy groups and physicians. We believe that the resulting alignment of informed stakeholders from an earlier stage will contribute to the drug's optimal clinical use and commercial success.

Improving the economics of development

The traditional development model is lengthy and

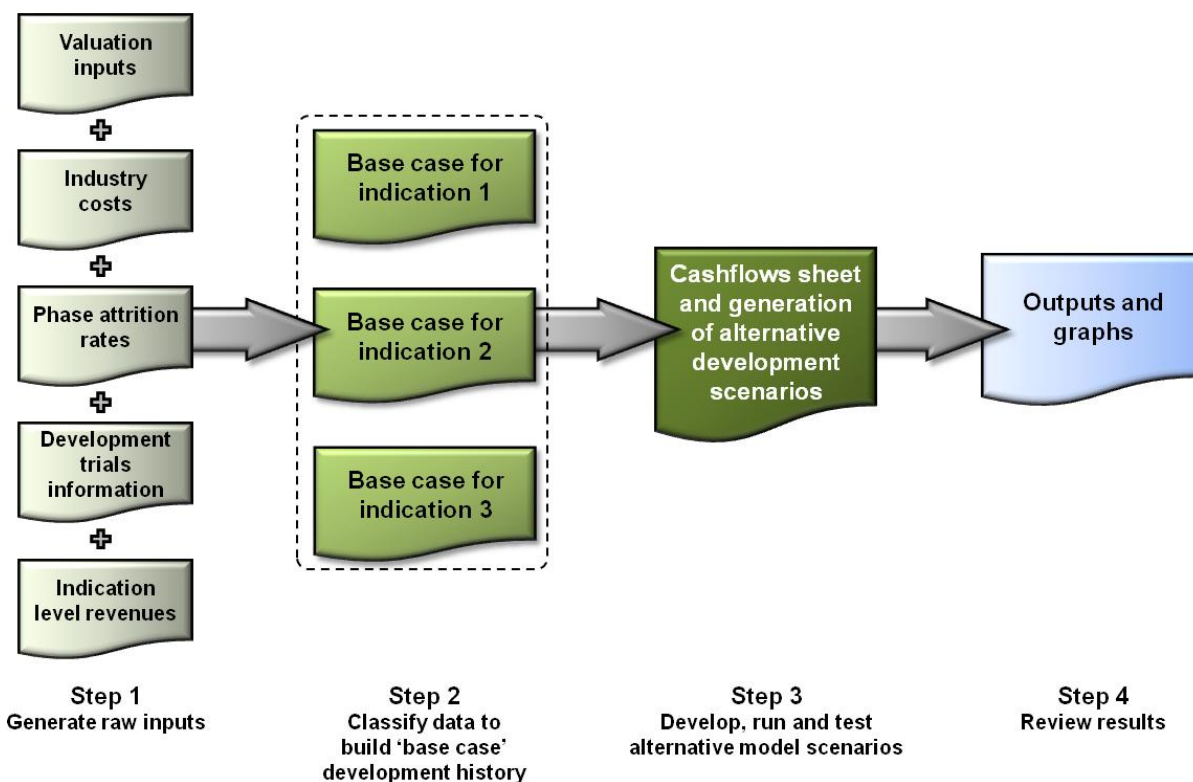


Figure 3: Schematic of Kinapse Real World Development financial model

expensive, typically taking 12 years and investment of \$1 billion or more (including the cost of failures). This is expected to rise even further. High attrition rates between early and late stages of product development means that only 5% of compounds tested will ever become therapeutically established, and fewer genuinely new products are coming to market. The current model therefore carries very high financial risk due to its inherent uncertainty and the delayed and expensive characterisation of clinical, regulatory and commercial risks that can threaten the success of the product. Late stage failure due to regulatory concern or an inability to secure an acceptable price/reimbursement is common. As the model is essentially linear (with key stages of pre-clinical, clinical, regulatory and value assessment occurring in sequence) and relatively fixed, the development plans of today limit the ability to react to unexpected findings and manage contingencies.

The Real World Development approach can obviate these risks and deliver a commercially viable development outcome. To support the financial case for, and planning of, Real World Development, Kinapse has developed a proprietary financial model to investigate the economic benefits associated with this new paradigm. This data-driven model (**Figure 3**) allows for a range of different development programme scenarios to be explored, and supports management decisions on investment in the Real World Development approach. The main features of our model are:

- Assessment and evaluation of individual trials based on data from public sources or real world data for actual trials provided by the pharmaceutical company sponsor
- Utilisation of standard industry costs, cycle times, attrition rates and sales curves generated from public sources, or company-specific data for these variables
- Incorporation of customisations based on client-specific requirements e.g. in clinical trial cycle times, costs, patient numbers, etc. to be applied in order to understand their impact on the project value to create bespoke modelling conditions or outcomes analysis
- Rendering alternative Real World Development scenarios for comparison between each other and the current development plan
- Application of changes to clinical trial times, costs, patient numbers, etc. to be applied in order to understand their impact on the programme's value
- Generation of cash flow profiles and programme valuations for different development scenarios.

Indicative modelling of several existing drug development programmes indicate substantial benefits of the Real World Development model accruing from:

- Earlier commercial use of the product resulting in earlier sales in a longer period of patent exclusivity
- Leaner Phase IIIa pivotal trial to fund real world methodologies in parallel
- Reduced overall development, and marketing and sales expenditure.

Implementing Real World Development

Real World Development builds on existing precedents, which indicate our approach can be implemented. These include the use of adaptive trial designs, as approved by the Food and Drug Administration (FDA), and the conditional approval of products that has been enabled by the European Medicines Agency Committee for Medicinal Products for Human Use (EMA CHMP). Similar models have also been explored and tested in other jurisdictions.

Adaptive trial design allows for studies to undergo in-trial modification and adaptation, enabling comprehensive exploration of promising developments. The use of multiple cohorts can be expanded upon once effective dosing has been determined. Adaptive designs also provide for interim evidence of the benefit and risk of the product to be assessed and encourage the exploration of stratified patient populations where the drug has shown initial benefit. Adaptive designs accommodate the early termination of a trial if clinical efficacy is not being demonstrated or safety issues have been identified, so reducing risk of harm and considerable downstream expense.

Conditional approval for innovative products is granted for up to one year through the European Centralised Procedure, but can be revoked at any point during this time. The FDA also grants accelerated approvals to those medicines that provide therapeutic advantage over existing treatments for life-threatening diseases with no validity period although full approval is granted once longer-term safety and efficacy is established. In general, the trend in Europe and the US is to require greater post-approval commitments including the use of a range of tools to control and manage risks identified during development and the approval process.

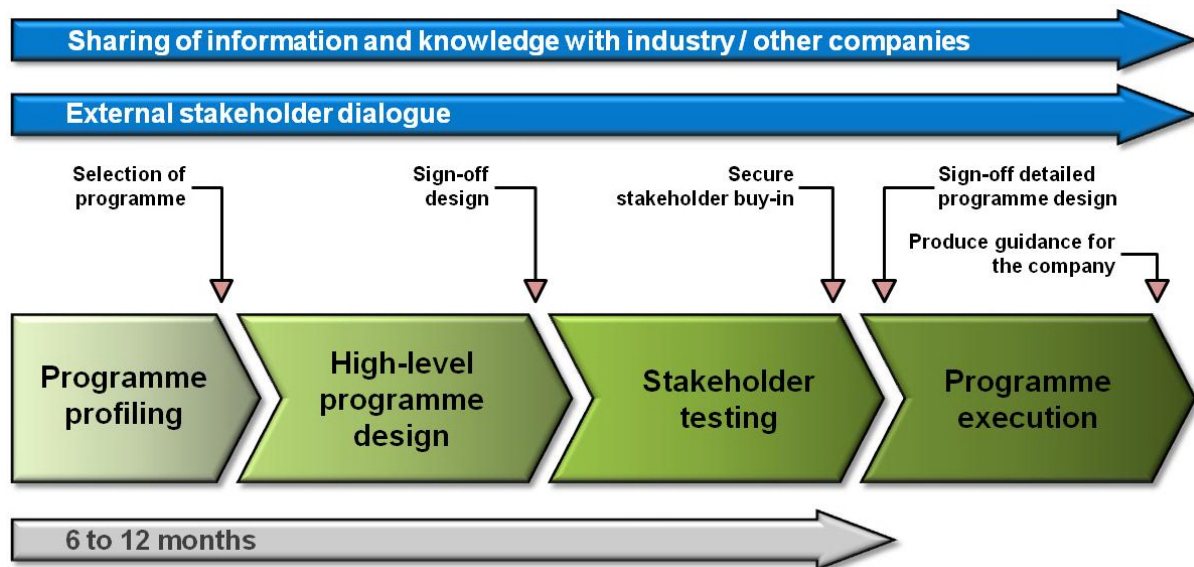


Figure 4: Kinapse approach to executing a Real World Development pilot

In July 2009, the UK government-sponsored Office for Life Sciences (OLS) acknowledged the need to transform the market entry of innovative medicines. OLS proposed the inception of an 'Innovation Pass' for such products. This is a 3-year conditional approval endorsed by the UK HTA body, the National Institute for Health and Clinical Excellence (NICE), aimed at those drugs that have the potential to deliver improved patient outcomes despite little or no demonstration of cost-effectiveness (which would previously preclude HTA approval) due to the limited target patient group or other clinical factors. OLS also recommended increased dialogue between the pharmaceutical company sponsor and NICE on the emerging value case.

Enabling processes and technologies include in-stream working with clinical study data sets and the extensive utilisation of electronic data management approaches underpinned by direct analysis of high quality electronic medical records (EMR). Large clinical research sites and regional networks are increasingly able to accommodate direct extraction of data from EMR. For instance, this is becoming a notable strength in the UK through the Connecting for Health initiative, which is providing consistent electronic medical records for the entire population. We believe that in the coming years many more sites and networks will adopt electronic medical records of sufficient quality to enable Real World Development, and that all stakeholders should support this adoption for the general public health benefits they will bring.

Getting started on the journey

Building on our financial model, we have developed a pilot approach (Figure 4) to initiating a Real World Development programme. There are four components to this pilot:

- **Programme profiling:** identifies a programme for Real World Development
- **High-level programme design:** establishes an outline programme design to enable stakeholder dialogue
- **Stakeholder testing:** seeks to refine the high-level programme design to secure stakeholder buy-in of both internal (functional and executive teams) and external groups (HTAs, regulatory bodies, external opinion leaders and patient groups)
- **Programme execution:** uses a 'learning lab' approach whereby lessons from the pilot inform, improve and optimise subsequent trial designs.

Our analysis suggests that Real World Development approaches are most easily applicable to programmes which:

- Are regionally-focused to simplify the coordination of regulatory and HTA organisations
- Have modest clinical or operational risk due to the nature of the drug, patient population or clinical sites
- Bear limited commercial risk (based on target indication and its lifecycle stage)
- Allow for contingencies should the programme need to revert to a traditional model.

Conclusion

The adoption of Real World Development on a large scale requires many strategic and operational challenges to be successfully addressed, but we believe that this is a necessity in the current industry climate. At Kinapse, we believe that the potential benefits of this strategy are substantial: earlier access of innovative medicines to patients, improved value for industry stakeholders, better decision making and management of benefit/risk, and lower development costs. We continue to develop our Real World Development model in conjunction with industry stakeholders as a part of our commitment to enhance the value that new medicines deliver to society. We welcome ongoing dialogue with all stakeholders to bring about such a model for drug development.

About the Authors

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About Kinapse

Kinapse provides consulting and outsourcing services to the life sciences industries, globally.

Our mission statement is: '*Collaborating with our clients to innovate for exceptional results*'. Kinapse clients include many of the world's leading pharmaceutical, biotechnology, medical device and specialty pharmaceutical companies, government organisations and life sciences service providers.

Our key advantages are:

- Focus on the life sciences industries
- Deep industry experience and technical acumen
- Proven blended onshore-offshore delivery model
- Track-record of innovative solutions and results

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