

Fast-to-patient:

Creative strategies for quick demonstration of clinical proof-of-concept

Author

J Fred Pritchard, Vice-President, Drug Development Services, Celerion

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Abstract

Interest in 'fast-to-patient' strategies is driven by the need to get to the clinical proof-of-concept decision as quickly as possible. It is this decision point that adds potential real value to a new drug candidate. Clinical pharmacologists, statisticians and regulators are involved in developing more efficient creative designs that employ adaptive trial strategies and that address several questions with fewer studies and subjects. Learning from years of oncology drug development forms a basis for enrolling cohorts of patients suffering from other diseases into dose escalation designs. Key to success is using existing and rapidly emerging technologies to enrich early clinical research studies with appropriate biomarkers of drug activity or impact on disease. A focus on programme planning and oversight will be needed to ensure proper execution of these more complex studies, in order to realise the potential time savings in getting to clinical proof-of-concept.

The expression 'fast-to-patient' has been coined to reflect a general philosophy that testing a new drug in a target patient population as quickly as possible is a key axiom of efficient early drug development. Fast-to-patient strategies focus on how to efficiently get to the 'clinical proof-of-concept' study, a key decision gate in determining whether or not to progress the drug further in

development. To make an intelligent decision, enough evidence must be presented that the drug is working in humans as hoped or predicted from preclinical work. Usually, these data must be collected in patients suffering from the disease targeted by the drug.

The definition of what constitutes 'clinical proof-of-concept' will vary depending on the criteria set by the key decision-makers. However, the common question being addressed is 'how much evidence on whether the drug is working in humans as planned is enough to trigger further investment in the product?' Once the agreed decision criteria have been met, the new drug has finally acquired real potential value. Value can be objectively measured either in terms of:

- What someone would be willing to pay for the product if it were for sale (current market value)
- How much additional money the owners and financial backers would be willing to invest in the product for further clinical development (committed investment)
- The product's priority within a portfolio of drug candidates (comparative status).

Many companies involved in early drug development do not have the resources to take a product all the way to market application and approval. Their business model is to capture a return on investment when the product acquires real potential value, usually by demonstrating clinical proof-of-concept. Figure 1 illustrates typical costs for getting an uncomplicated small molecule product through key early drug development decision gates. Also shown are typical average values that other developers or investors would be willing to pay for a product of interest at each of these decision gates. Usually, there is little return on investment (value/cost) until a product can show some indication of efficacy in patients. Then, return on investment can range from three- to 20-fold or higher. Interestingly, this broadly matches and rewards the risk that developers face with successfully

bringing new drug candidates into the later stages of clinical development.

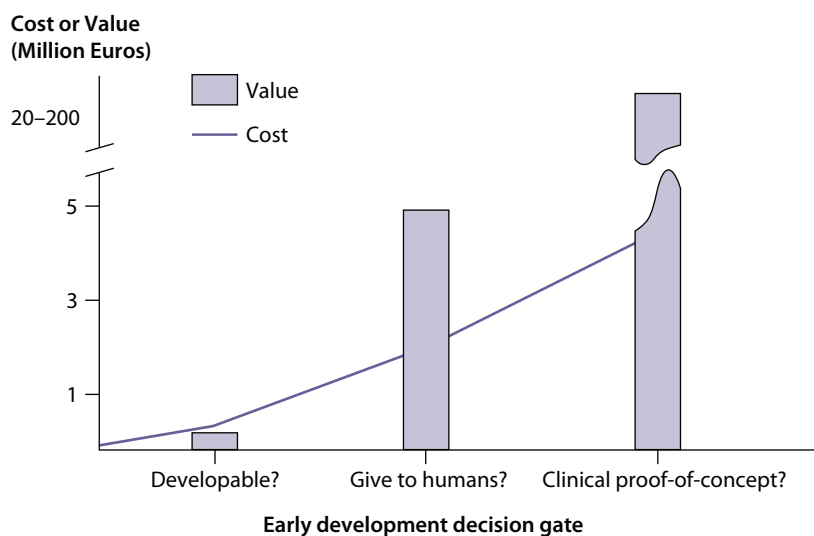
During the 1980s and 1990s, early clinical development programmes of small molecules, as opposed to biologicals, consisted of a series of safety and tolerability studies starting with single ascending dose (SAD) design until a maximum tolerated dose (MTD) was obtained, followed by multiple ascending dose (MAD) designs that established safety and tolerance in the desired pharmacological dose range over a short dosing interval of several days. Pharmacokinetic information helped to establish inter-subject variability in drug delivery, any associations of exposure with undesired effects and whether or not an appropriate and predictable dosing regimen existed. These data provided the foundation and rationale for the design of the first study in patients. However, this step-by-step approach often took up to two years before any information from patients dosed with the drug became available.

Pushed by pressure to make drug development more efficient in time and direct cost, more creative strategies have emerged since 2000. These include combination SAD/MAD designs as well as SAD/MAD designs with arms to test for food effects and drug-drug interactions. More recently, patient cohorts are being included in SAD/MAD combination studies with the goal of collecting more relevant safety and tolerability information as well as enhancing the chance of getting early signals of efficacy.

Adaptive and creative designs in early clinical research

Adaptive designs involve the ability to review data at certain pre-identified times during the study conduct, in order to make adjustments of sample size; reduce or increase numbers of subjects per treatment arms; modify dose levels; or drop or add treatments. Statistical 'penalties' are added to accommodate the potential bias introduced by such early

Figure 1: Typical cost and potential market value of drug candidates during early development



Source: J Fred Pritchard – informal survey of vendors and venture capital firms 2003 and updated in 2006 and 2009.

knowledge of the data, in the confidence of the eventual conclusions generated by the study. While these approaches have gained popularity as a way of enhancing the efficiency of large clinical trials involving hundreds of patients, there is growing awareness of the utility of applying adaptive-like statistical principles to smaller early clinical trials.¹

Combining SAD/MAD objectives and incorporating cohorts of patients in Phase I studies have been referred to as 'creative', 'fusion' or 'agile' design.² These studies involve many decisions made mid-study to adjust dose, change the number of subjects receiving a certain dose, or stop a treatment, and so share many of the features of adaptive designs. Adding more statistical rigour into the assessment of MTD in early human trials has been a focus of statisticians over the past few years.^{3,4}

Learning from oncology studies

Creative designs involving patients have largely been influenced by years of drug development work in oncology patients where safety testing of cytostatic and cytotoxic agents cannot be ethically performed in healthy subjects. In this situation, all the safety, tolerability and pharmacokinetic (PK) goals for a clinical Phase I programme must be done in patients. The key challenge in incorporating patients into early trials is how to decipher drug-related signals of safety from the background of effects produced by the disease itself or other

concomitant medications. In addition, unlike studies in healthy subjects, patients want to have some chance that the therapy might be helpful in alleviating their disease. So at the heart of early clinical research of new oncology treatments are study designs that minimise the number of patients who may be underdosed and therefore would not benefit from the therapy, while limiting harmful toxicities in these fragile people.

Traditional Phase I oncology study designs escalate dose in a predetermined scheme after treatment of every three or four patients until the first sign of a potentially problematic toxicity is observed in one or more patients. The investigators then may agree to reduce the dose slightly and treat more patients to see if the toxicity occurs in other patients at this dose. If no additional limiting toxicity is observed, the dose escalation is resumed until reproducible dose-limiting toxicity is evident in more than one patient at a given dose, or the desired pharmacological exposure has been achieved. Although this 'up-and-down' dose design is a reasonable approach to home in on MTD while ensuring patient safety, it has recently been estimated that only around 35% of patients entered in such trials end up within a range of pharmacologically active doses.⁵ Adaptive dose-escalation designs using Bayesian statistical approaches appear to be more effective, with around 55% of the treated patients predicted to be within a pharmacologically effective range.⁵

Bayesian approaches for dose ranging involve either the continuous reassessment method (CRM) or logistical regression models.^{6,7}

These approaches, born in the oncology research environment,⁸ are now being considered more generally across therapeutic areas as more patient cohorts are included in early clinical research. A few examples of such studies, published in the recent literature, are listed in Table 1. As with oncology research, creative designs may be particularly helpful for other challenging patient populations (eg, ALS, stroke). Moreover, the authors' conclusions support a growing belief among clinical pharmacologists that adaptive-like, creative or agile approaches can save time and resources, thereby making early clinical development more efficient.²

Enablers of more creative study designs

Today, creative designs are augmented by an expanding universe of biomarker technologies that embody multi-analyte platforms, microsampling, imaging, genomic analysis, and high capacity data analysis. More and more, these technologies allow us to gather indications of drug effects (pharmacodynamic biomarkers) or mechanism of action early in clinical development, often during the first human studies. In addition, biomarkers can also enable assessment of key off-target effects of new drug candidates (safety biomarkers) that may be important to know before progressing the drug further into clinical development.

Regulatory authorities have become much more open to considering non-traditional early clinical designs. Efforts such as the US FDA's Critical Path Initiative (see <http://c-path.org>) have focused attention on the use of adaptive designs in clinical drug development. While these approaches have traditionally applied to later stage clinical studies, the objectives of early clinical research lend themselves to designs where knowledge from one part of the study drives how subsequent portions of the study will be executed. Enriching early studies with relevant biomarker information has further justified creative or adaptive approaches, especially if it involves a patient cohort where very relevant information about the drug's actions can be obtained earlier in the process than is possible with more traditional paradigms.

Technological advances in data capture and management (eg, electronic data capture systems) as well as modern computational software and methods for statistical analysis (eg, PK/PD modelling and simulation methods)

Table 1: Examples of published studies utilising adaptive-like designs in early clinical research studies of non-oncology drugs

Drug	Disease target	Design	Biomarker or endpoint	Comments	Reference
CoQ10	Amyotrophic Lateral Sclerosis (ALS)	High dose for 9 months Part 1: n=35/gp, 1.8 vs 2.7 g/day Part 2: n=75/gp 2.7g/day vs placebo	ALS function rating scale	Adaptive design showed no benefit of CoQ10 in ALS function ratings over 9 months. Prevented need for large Phase III study	P Kaufmann <i>et al. An Neurol.</i> 2009; 66(2) 235-44.
Lovastatin	Acute stroke	High dose for 3 days Dose escalation (1-8 mg/kg/day)	Hepatotoxicity and myotoxicity	7-13% toxicity reached at 8 mg/kg/day. High doses for 3 days after stroke safe.	M S Elkind <i>et al. Cerebrovasc Disc.</i> 2009; 28(3): 266-75
CS-0777 (sphingosine 1-phosphate receptor modulator)	Immunomodulator	PK/PD model developed from monkey data – applied to SAD and MAD study and updated after each dose escalation	Lymphocyte counts, later key lymphocyte subset counts for MAD studies	Imax of 85% achieved, IC ₅₀ determined. Less time and fewer subjects than traditional designs	S Rhotatagi <i>et al. J Clin Pharmacol.</i> 2009. 49(1):50-62
BIBN 4096 BS (calcitonin gene-related peptide receptor antagonist)	Migraine headache	SAD (placebo, 0.25, 0.5, 1, 2.5, 5, 10 mg iv – group sequential adaptive treatment assignment (n=126)	Pain-free response rate, secondary pain measures, adverse events (AE)	2.5 mg dose selected (response rate = 66% vs placebo = 27%; AE rate 20% vs placebo 12%)	J Olesen <i>et al. New Engl J Med.</i> 2004. 350(11):1073-75
R411 (dual alphasbeta1-alpha4beta7 integrin antagonist)	Chronic asthma	Combined SAD/MAD plus active metabolite IV/PO absolute bioavailability (n=132)	PK R411 and active metabolite, AE	Safety and linear PK established up to 900 mg – design saved time	Y Hijazi <i>et al. J Clin Pharmacol.</i> 2004 44(12):1368-78

have contributed to the evolution of creative study designs. These advances have enabled valuable interim data analysis to be available quickly, allowing for adaptive design and decision-making during the course of a study.

Another driver for more creative early clinical study designs has been the success in the late 1990s and early 2000s of some emerging pharmaceutical companies in building new products around innovative technology and getting to clinical proof-of-concept with minimal investment of time and money, often incorporating fusion designs and/or biomarkers into their early clinical development programmes.

Finally, large pharmaceutical companies have joined the chorus of proponents of speedier and more cost-effective early clinical development. While the industry has enjoyed accelerated drug discovery in recent years, the impact of this on delivery of new novel drugs to patients has become muted in the clinical phase by rising development costs, increased requirements by regulators before granting marketing approval, and a risk-adverse environment by management

for introducing novel medicines after costly market withdrawals of some commercially successful products. For example, the removal of several effective COX-2 inhibitor drugs from the market because of cardiovascular safety concerns greatly increased the cardiovascular safety testing in the clinical development of all new drugs as requirements for registration. Cardiovascular safety strategies involving sophisticated cardio monitoring and assessment have since emerged, but at a significant cost to drug development. With continuing forces escalating drug registration costs it becomes more imperative for the industry to pick the right drug to take into later clinical development. This further fuels the need to get new drug candidates quickly to clinical proof-of-concept studies where their potential value can be identified using the best tools, designs and knowledge available.

Enriching strategies that enable fast-to-patient approaches

While adaptive-type designs can speed up the execution of dose escalation strategies, early drug development programmes can

be enhanced by enriching the information gathered from the first few humans who receive a new drug.

Animal models that more aptly reflect the clinical situation can be critical to guiding which drug candidates are put forward for full preclinical development. An example of improved preclinical to clinical translation is the rethinking of study designs in animal models of occlusive stroke. Most patients do not get treatment for stroke until several hours after the vascular occlusion occurred and the timing of drug dosing in animal models now reflects this reality. Moreover, new tests for rodents have been designed that measure fine motor functioning, thereby better reflecting the functionality in affected limbs of humans who suffer debilitating stroke. The key principles guiding recent discovery work in animal stroke models are articulated in the STAIR criteria (see <http://thestair.org/>). Collectively, these efforts have changed the focus for stroke research, with emerging interest in treatments that promote neurogenesis and repair.

In many instances no attempt is made at the time to get an estimate of the blood, plasma

or tissue concentrations of a new drug in the animal model where it shows pharmacological activity. Modern liquid chromatography–mass spectrometry (LC/MS) technologies enable rapid development of ‘qualified’ assays that can measure drugs in small volumes of blood or tissue. Such measures of systemic exposure can be very useful when attempting to justify a target pharmacological dose range in humans through PK modelling and inter-species scaling.

Currently, there is a push to include cohorts of mildly affected patients in Phase I safety/tolerability/PK studies. However, unlike the oncology environment, these studies seek patients with mild, stable disease or those newly diagnosed and naïve to other treatments so that the cleanest assessment of safety, tolerability and PK can be made. Therefore, patients must agree to participate in a study that is short-term and where there is little chance of deriving any benefit from the treatment at a time when they may be seeking more robust options for therapy. For more slowly progressing diseases there are often subjects with ‘pre-disease’ conditions that are believed to predispose them to an eventual firm diagnosis. For example, people with mild cognitive impairment have a greater likelihood of progressing to a diagnosis of Alzheimer’s disease with time. These individuals may be a good population to study safety and tolerability of potential treatments for Alzheimer’s disease as a safety bridge to the 6-12 month studies in patients needed to demonstrate clinical proof-of-concept.

To harness the power of novel biomarkers, sufficient time must be planned to develop robust methods suitable for use in early human research. The rapidly emerging universe of biomarker technologies provides the opportunity to develop ways of measuring the effect of disease and the impact of drug therapy on parts of biochemical pathways, receptors, protein–protein interactions, tumour or tissue lesion volumes, quantifying specific cells that carry specific receptors, enzymes, genes or other components of the targeted biology. However, even with sophisticated technology it can take several months to create an assay that is appropriately cost-effective, selective and sensitive to be included in early clinical trials. Nevertheless, these technologies offer ways to follow the ‘systems biology’ in humans of new drugs, and may be the only way to establish clinical proof-of-concept in the first few patients to receive the drug.

If the new drug candidate works against a target that has been previously studied in

the clinic, then leveraging this knowledge and available biomarkers can speed up the time it takes to get the drug into patients.² Investigators, ethics committees and regulators are much more agreeable to strategies that incorporate patient cohorts into MAD designs if there is comfort in knowing that this target has been safely challenged with previous similar drug therapy.

A reality of including patients earlier in clinical drug development is dealing with the presence of concomitant drug therapy. It is becoming more and more difficult to find patients who are not taking other medications or who can stop their therapy while on study. It is standard practice today to have a reasonable knowledge from *in vitro* preclinical work of which drug-metabolising enzymes or drug transporters are likely to be involved in the clearance of the drug from the human body prior to ever giving the drug to people. If the drug is expected to be highly metabolised by enzymes that have known genetic polymorphisms (eg, CYP2D6, CYP2C9, CYP2C19), then genotyping the first hundred or so subjects enrolled in Phase I studies can be a valuable, yet cost-effective, study enrichment strategy. There are known frequencies of these polymorphisms in various human populations. One can compare the PK profiles obtained from those who turn out to carry a functionally effective mutation to see if they are outliers in terms of clearance, half-life or peak plasma concentrations. If not, then it is unlikely that any other drug that inhibits or competes for metabolism by that particular pathway would also have much effect on the clearance and distribution of the new drug candidate. Thus, a rationale can be developed to allow patients taking certain drugs into early clinical trials with a low risk of confounding the study output with an interfering drug–drug interaction.

Challenges in executing fast-to-patient strategies

As noted above, the opportunity to employ a fast-to-patient strategy depends on the novelty of the drug target, the type of patient population proposed for the therapy, the safety profile of the drug or drug class, and the availability of biomarker tools that can enrich the information coming from early studies in humans beyond just safety, tolerability and pharmacokinetics. If conditions are right, an adaptive-type or creative design can provide a rapid way to progress to patients. However, this approach presents several challenges. The

protocol becomes complex with several parts encompassing a spectrum of objectives and analyses. As a result, the fusion study is much more costly than individual traditional Phase I studies where the objectives are more narrowly focused. The pressure for rapid decision-making requires fast turnaround of data (bioanalytical, safety, PK) in order to progress through the dose escalation plan. The execution of the protocol may require collaboration between two or more principal investigators and sites in order to meet timelines and patient recruitment. The complexity of protocol in the initial IND submission may generate regulatory questions that could slow down study start. Finally, formal reporting of the first parts of the protocol cannot proceed until the last parts of the protocol are completed, the data cleaned and the database locked.

Despite these challenges, information from creative study designs involving patients early in clinical development can expedite decisions about the real potential value of a new drug candidate. In this way, the ongoing evolution of fast-to-patient approaches is an important component in improving the efficiency of early drug development.

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