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Teaser This article describes key aspects for enhancing the rigour and efficiency of clinical proof-of-concept trials, to enable sound and cost-effective investment decisions.

Opportunities and pitfalls in clinical proof-of-concept: principles and examples

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Clinical proof-of-concept trials crucially inform major resource deployment decisions. This paper discusses several mechanisms for enhancing their rigour and efficiency. The importance of careful consideration when using a surrogate endpoint is illustrated; situational effectiveness of run-in patient enrichment is explored; a versatile tool is introduced to ensure a high probability of pharmacological success; the benefits of dose-titration are revealed by simulation; and the importance of adequately scheduled observations is shown. The general process of model-based trial design and analysis is described and several examples demonstrate the value in historical data, simulation-guided design, model-based analysis and trial adaptation informed by interim analysis.

Chao Chen has over 20 years of experience in pharmaceutical research and development. Currently, he leads a team of quantitative clinical pharmacologists in multiple disease areas at GlaxoSmithKline, where they use mathematical and statistical modelling and simulation to conduct nonclinical to clinical translation of pharmacokinetics and pharmacodynamics, to understand disease progression and dose–response properties, and to optimise trial design and dose selection. His research focuses on enhancing the success of drug development and registration through effective knowledge integration, efficient trial design and informative data analysis.

Introduction

Clinical drug development is a lengthy and costly business. On average, bringing a molecule from its first human trial to marketing application takes 10 years; and the average cost has nearly tripled over the past two decades to be higher than US$2 billion [1,2]. It is also a high-risk business. The phase-to-phase transition rates are 64% (I–II), 32% (II–III), 60% (III to marketing application) and 83% (regulatory approval), resulting in a low overall success rate of 10% [2,3]. Phase II typically includes a clinical proof-of-concept trial (PoC) followed by dose-finding (although the PoC can be an opportunity for generating dose–response data). For an experimental medicine, the PoC is typically a small trial in short duration, to generate sufficient evidence on efficacy and safety for the relevant patient population, to inform the decision about whether further and large investment should be made to continue the development of the medicine. The size and duration of a PoC vary by indication, from a single-arm small study measuring overall response of a refractory solid malignancy tumour in a small number of patients to a 3-month controlled study of HbA1C and weight loss in <100 patients with type-II diabetes or a 2-year controlled study assessing motor function in hundreds of patients with Parkinson's Q2 disease.

Other operational terms are used to describe early clinical trials, without a widely agreed official definition. 'Proof of pharmacology' and 'proof of mechanism' usually refer to experiments for generating clear pharmacological evidence where engaging the target by the drug molecule

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causes intended changes in the mechanism pathway. Their positive results do not necessarily mean clinical efficacy, because the pathway and its pharmacological perturbation might not be sufficiently important to the disease. Another term: 'proof of principle', is sometimes used interchangeably with proof of mechanism and proof of pharmacology.

The particularly low 32% transition rate from Phase II to III therefore poses several questions. Was the entry to PoC by some assets not warranted? Was the failure of PoC by some assets not justified? For those that passed the PoC but failed in the subsequent dose-ranging trial, was the PoC conducted with sufficient rigour? In other words, how to design and analyse a high-quality PoC and analyse the results to reach a firm conclusion?

Inherent low success rate

Before answering the questions, the inherent high risk for a clinical PoC should be acknowledged and the main driver behind this risk should be understood. The clinical PoC is usually the first opportunity in a drug development programme where evidence of efficacy in patients is evaluated. It is important to recognise that, given the low predictive value of clinical efficacy of data from *in vitro* experiments, animal models, human disease models and human biomarkers that inform the PoC, a high false-positive rate for clinical PoC is expected. This can be demonstrated by some simple statistics as described below.

Under a reasonable assumption that 10% of the hypotheses informed by pre-PoC evidence would be valid for human therapeutics, the expected positive trial rate and its reliability can be assessed in various scenarios of power (correct positive) and Type I error (i.e., false-positive) levels that are associated with the design of 1000 PoCs, each based on a different hypothesis (Table 1). The calculations show that, for the usual power and false-positive levels, the proportion of positive trials is expected to be low and only one-third to two-thirds of the positive trials are true positives. By contrast, the reliability for the negative findings is likely to be high: from 99% to 96%. These simple calculations illustrate the inherent high risk for false-positive findings in a clinical PoC regardless of the Type I error level set for the trial, owing to the dominant effect of the high base-rate of the invalid hypotheses. When the proportion of the valid hypotheses is increased to 20%, the number of positive trials and, more importantly, the reliability of the positive findings go up. These findings highlight the importance of rigorous target selection.

Therefore, every effort should be made to understand the relevance of the drug–target pathway to the human disease, the importance of the target in that pathway, the pharmacokinetic and pharmacodynamic properties of the molecule, the nature of the interaction between the target and the molecule, and the extent of target pharmacology. These efforts aim at reducing the base rate of the false-positive trials. Although the pharmacokinetic (such as bioavailability and clearance) and pharmacodynamic (such as potency and selectivity) properties, as well as the mechanism of action (such as receptor modulation) of the molecule, can be designed and optimised by pharmaceutical chemistry approaches, good understanding of the pathway relevance and sound target validation for human disease are essential for the success of a pharmacological intervention [4,5]. With this understanding, this paper focuses on several key aspects on PoC design and analysis.

Key aspects for enhancing rigour and efficiency

Many important questions need to be answered about the design of a PoC. They include: whether a regulator-accepted endpoint or a surrogate should be used; how diverse or selective the patient population should be; which drug dose(s) should be tested; when the key endpoint will be measured; what the minimal effect size is that must be detectable; what the tolerable false-positive and false-negative levels are; which statistical methods would be appropriate for result analysis to maximise the confidence in the findings; whether interim analyses should be conducted and how their results will be used; and whether there is a way to seamlessly transition a PoC into dose ranging to gain confidence, save time and patient numbers. Some of these issues are linked; hence so are the answers. For example, the observation schedule should be optimal for the intended analytical approach. Because of the high uncertainty about clinical profile of the compound at the PoC stage, elements such as drug dose, sample size, treatment duration or observation schedule, and even trial population, could be adapted based on findings from interim analyses conducted during the trial to increase the likelihood of success.

TABLE 1

The low true-positive rate for proof-of-concept trials due to the lack of validity of the driving hypothesis

Type I error	Power	If 10% of the hypotheses are valid				If 20% of the hypotheses are valid			
		No. of true +	No. of total +	% of true +	% of true −	No. of true +	No. of total +	% of true +	% of true −
0.05	0.9	90	135	67	99	180	220	82	97
0.05	0.8	80	125	64	98	160	200	80	95
0.05	0.7	70	115	61	97	140	180	78	93
0.10	0.9	90	180	50	99	180	260	69	97
0.10	0.8	80	170	47	98	160	240	67	95
0.10	0.7	70	160	44	96	140	220	64	92
0.15	0.9	90	225	40	99	180	300	60	97
0.15	0.8	80	215	37	97	160	280	57	94
0.15	0.7	70	205	34	96	140	260	54	92

Expected positive (+) and negative (−) PoC rates are calculated for 1000 trials each testing a different hypothesis, at levels of Type I error (0.05–0.15) and power (0.7–0.9) that are commonly employed in proof-of-concept trials. When only 10% of the hypotheses are valid for human efficacy, the numbers of positive trials were small (ranging from 115 to 225), and the proportions of the truly positive trials were low (ranging from 34% to 67%). When the proportion of the valid hypotheses increases to 20%, the corresponding ranges both increase – to 180 to 300 trials and 54% to 82%, respectively. By contrast, the reliability for negative findings is consistently high.

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