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Innovative approaches to clinical development and trial design

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Summary. Pharmaceutical innovation is increasingly risky, costly and at times inefficient, which has led to a decline in industry productivity. Despite the increased investment in R&D by the industry, the number of new molecular entities achieving marketing authorization is not increasing. Novel approaches to clinical development and trial design could have a key role in overcoming some of these challenges by improving efficiency and reducing attrition rates. The effectiveness of clinical development can be improved by adopting a more integrated model that increases flexibility and maximizes the use of accumulated knowledge. Central to this model of drug development are novel tools, including modelling and simulation, Bayesian methodologies, and adaptive designs, such as seamless adaptive designs and sample-size re-estimation methods. Applications of these methodologies to early- and late-stage drug development are described with some specific examples, along with advantages, challenges, and barriers to implementation. Because they are so flexible, these new trial designs require significant statistical analyses, simulations and logistical considerations to verify their operating characteristics, and therefore tend to require more time for the planning and protocol development phase. Greater awareness of the distinct advantages of innovative designs by regulators and sponsors are crucial to increasing the adoption of these modern tools.

Key words: clinical trial, pharmaceutical preparations, drug approval.

Riassunto *(Approcci innovativi allo sviluppo clinico e al progetto di sperimentazione)*. L'innovazione farmaceutica è sempre più rischiosa, costosa e a volte inefficace, il che ha portato ad una diminuzione della produttività industriale. Nonostante l'aumento degli investimenti nella ricerca e sviluppo da parte delle industrie, il numero delle nuove molecole che raggiunge l'autorizzazione per l'immissione sul mercato non è in aumento. I nuovi approcci allo sviluppo clinico e al piano di sperimentazione potrebbero avere un ruolo chiave per il superamento di alcune di queste sfide, attraverso il miglioramento dell'efficacia e la riduzione delle misure di *attrition*. L'efficacia dello sviluppo clinico può essere migliorata attraverso l'adozione di un modello più integrato che aumenti la flessibilità e massimizzi l'utilizzo di una maggiore conoscenza. Cruciali per questo modello di sviluppo di farmaci sono i nuovi strumenti, inclusi i modelli e la simulazione, le metodologie bayesiane e i progetti di adattamento, quali i disegni adattativi continui ed i metodi di rivalutazione della dimensione del campione. L'applicazione di questi metodi alla fase iniziale e finale dello sviluppo del farmaco è descritta con alcuni esempi specifici, insieme ai vantaggi, alle sfide e alle barriere all'implementazione. A motivo della loro flessibilità, questi nuovi progetti di sperimentazione richiedono analisi statistiche significative, simulazioni e considerazioni logistiche per la verifica delle caratteristiche operative e pertanto tendono ad aver bisogno di maggior tempo per la fase di pianificazione e di sviluppo del protocollo. Una maggiore consapevolezza dei vari vantaggi dei progetti innovativi da parte degli enti regolatori e degli sponsor è essenziale per una crescente adozione di questi moderni strumenti.

Parole chiave: sperimentazione clinica, preparazioni farmaceutiche, approvazione di farmaci.

A NEW DEVELOPMENT PARADIGM

Pharmaceutical innovation is increasingly risky, costly and at times inefficient, which has led to a decline in industry productivity [1-3]. Estimates for the average cost of bringing a new drug to market range between $ 800 million and $ 2 billion, in which late-stage failures and the rising costs of Phase II and III trials represent key components [4-9]. Despite the increased investment in R&D by the industry, the number of new molecular entities achieving marketing authorization is not increasing. Novel approaches to clinical development and trial design could have a key role in overcoming some of these challenges by improving efficiency and reducing attrition rates.

The traditional approach to drug development separates clinical development into sequential, distinct phases, in which progress is measured at discrete milestones, separated by "white space". The ef-

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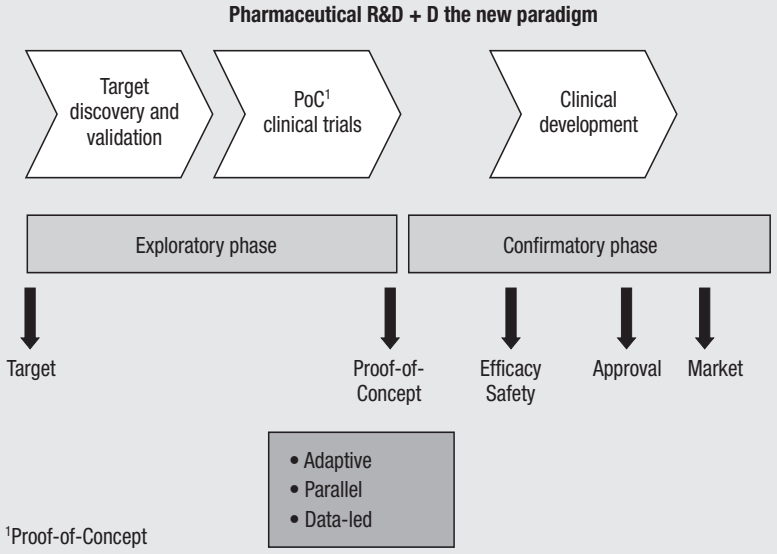

Fig. 1 | *A new paradigm for clinical development. During the exploratory phase of development, this new model uses all available knowledge and tools, including biomarkers, modelling and simulation, as well as advanced statistical methodology. Trials are designed to determine proof-of-concept (PoC) and to establish dose selection to a level of rigor that will enhance the likelihood of success in the confirmatory phase. During the confirmatory phase, modern designs, tools and knowledge are applied to larger-scale studies with the goals of identifying the target patient population in which the drug is efficacious, establishing the benefit/risk ratio and confirming the optimal dose and dosing regimen. During this phase, innovative clinical trial designs such as adaptive or seamless studies compress timelines, improve dose and regimen selection, and reduce the number of patients assigned to non-viable dosing regimens. Modified from [36]*

fectiveness of clinical development can be improved by adopting a more integrated model that increases flexibility and maximizes the use of accumulated knowledge. In this model, broader, more flexible phases leading to submission for approval are designated "exploratory" and "confirmatory" *(Figure 1)*. This model is adaptive, parallel and data-led, and allows all available knowledge to be appropriately shared across the breadth of development studies to improve the quality, timeliness and efficiency of the process. Central to this model of drug development are novel tools, including modelling and simulation, Bayesian methodologies, and adaptive designs, such as seamless adaptive designs and sample-size re-estimation methods.

MODELLING AND SIMULATION

Modelling is a key feature of the more integrated approach to drug development *(Figure 1)*. Biological modelling is used to understand genetic, biochemical and physiological networks, as well as pathways and processes underlying disease and pharmacotherapy [10, 11]. Pharmacological modelling guides clinical trial design, dose selection and development strategies [12, 13]. Finally, statistical modelling can be used to assess development strategies and trial designs in populations [10, 11, 14]. These three types of modelling should be used throughout the drug development process to maximize their synergies. Indeed, modelling and simulation activities are increasingly being used to support development strategies and health authority interactions throughout all phases of development [15-19]. In addition, the US Food and Drug Administration (FDA) is currently posting selected pharmacometrics reviews and guidance documents on its website [20].

An important goal of a drug development program is the selection of a dose and dosing regimen that achieves the target clinical benefit while minimizing undesirable adverse effects. Biological and pharmacological modelling can be very useful in this context [21, 22]. For example, we have used such modelling in the dose selection for canakinumab (Ilaris; Novartis), a monoclonal antibody that has recently been approved for the treatment of the rare genetic disease, Muckle-Wells syndrome *(Figure 2)*. Clinical data on the relationship between activity of the therapeutic target (interleukin 1), markers of inflammation and remission of symptoms were captured in a mathematical model that was continuously adjusted to fit emerging data. Simulation was then used to propose a suitable dose and dosing regimen to achieve the desired response for the majority of patients – in this instance, an 80% probability that 90% of patients would remain flare-free for 2 months. The data derived from this modelling exercise allowed for selection of a dosing regimen that was investigated and confirmed in a Phase III trial [23]. Similarly, modelling has been used to address regulatory queries at filing regarding dose justification for a new molecular entity. In this instance, integration of safety and efficacy data across all clinical trials in the drug development program allowed for robust and simultaneous assessment of benefit and risk.

BAYESIAN APPROACHES TO CLINICAL DEVELOPMENT

Bayesian methodology relies on the use of probability models to describe knowledge about parameters of interest (for example, the treatment effect of a drug in development). Bayesian inference uses principles from the scientific method to combine prior beliefs

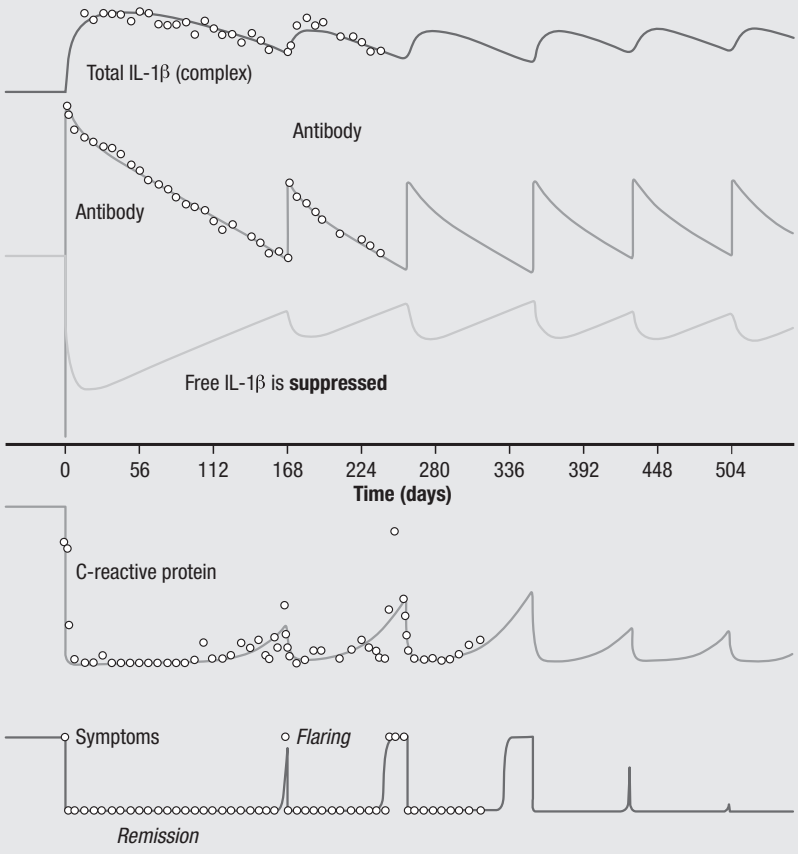

Fig. 2 | *A dose selection in the development of a therapeutic for Muckle-Wells syndrome. Muckle-Wells syndrome is a rare genetic disorder characterized by fever, urticaria, joint pain, and malaise. A monoclonal antibody against interleukin -1β (IL-1β), canakinumab, has been developed to treat such an IL-1-dependent inflammatory disease. The antibody is delivered parenterally and binds to free IL-1β, driving it into the inactive complex and leading to remission of symptoms [23]. Total IL-1β, which represents mainly the inactive complex, increases after dosing and can be measured. By the laws of mass action, the free and active form of IL-1β, which cannot be measured, must decrease. However, the reduction in free IL-1β results in a decrease in markers of inflammation, including C reactive protein (which can be measured), and a remission of clinical signs and symptoms of disease. The clinical data on these relationships can be captured in a mathematical model, shown in the figure, and is continuously adjusted in light of new data. This framework, simulation could then be used to propose a suitable dose and dosing regimen that would be predicted to produce a desired response for the majority of patients (for example, an 80% probability that 90% of patients will be flare-free for 2 months). Reproduced with kind permission from [36].*

with observed data, producing enhanced, updated information [24, 25]. Using Bayesian methodologies, initial beliefs about the parameters are summarized in their prior distribution. Then, new data values are collected experimentally and the probability distribution of these values leads to the likelihood function (the observed evidence on the parameters). The two elements are then combined, using Bayes' theorem, to produce the posterior distribution of the parameters – that is, the updated knowledge given the observed evidence. By contrast, frequentist methods rely solely on observed evidence for inferences, and typically do not formally take into account prior information.

Bayesian methods may enhance the traditional approach to power calculations for sample size estimates. By applying the posterior distribution to the traditional power curve, a more precise estimate of the underlying treatment difference can be obtained, as well as the probability distribution for the range of treatment differences that may be possible. This allows for a more precise and realistic estimate of the power calculation for a given sample size.

Bayesian approaches may also maximize the use of limited information available in a proof-of-concept (PoC) trial. Early development studies for establishing PoC often use small patient cohorts (10-20 subjects). These patients are typically observed for a relatively short period of time (several weeks) to evaluate early efficacy and safety signals, which are frequently measured on a continuous scale and observed several times over the duration of the study. However, the endpoints are typically based on a single time point and use dichotomized versions of the original variables to characterize responder and non-responder behaviour. There are, therefore, two types of information loss that often occur in PoC studies: the dichotomization of continuous endpoints and a failure to use all of the available longitudinal measurements collected in the study [24].

Because of small cohort sizes, only safety problems occurring in a relatively large percentage of patients can be reliably detected by dose-escalation procedures. Likewise, only relatively strong efficacy signals can be detected with reasonable statistical power. The detection of safety and efficacy signals can be made more efficient in various ways: by drawing on data and information external to the trial, and deploying longitudinal modelling approaches to make use of all available information. Furthermore, the utility of PoC studies within drug development programs can be enhanced by incorporating the information obtained in them directly into later-phase trials [10, 11, 16, 17]. Bayesian modelling techniques are particularly useful in implementing these approaches.

ADAPTIVE TRIAL DESIGNS

The core concept of adaptive trial design is that it uses accumulating data to decide on how to modify aspects of the study mid-trial, in a pre-planned manner, without undermining the validity or integrity of the study [25-28]. Possible adaptations include adjustments to sample size, allocation of treatments, the addition or deletion of treatment arms, inclusion and exclusion criteria for the study population, adjusting statistical hypotheses (such as non-inferiority or superiority), and combining trials or treatment phases. Adaptive trials have the potential to translate into more efficient drug development and better use of available resources.

Adpative approaches can be applied to both early and late development trial designs. In an adaptive dose-finding study [29, 30], the dose assignment(s) to the next subject, or next cohort of patients, is based on responses of previous subjects, and the dose assignment is chosen to maximize the information about the dose-response curve, according to some pre-defined objective metric (for example, variability in parameter estimates) *(Figure 3)*.

Efficiency can be increased through the use of seamless adaptive designs, which aim to combine objectives traditionally addressed in separate trials into a single trial [27, 31]. A specific example is the seamless adaptive Phase II/III design addressing objectives normally achieved through separate Phase II and III trials. The first stage of a seamless adaptive Phase II/III trial might be similar to a late-Phase II trial, with a control group and several treatment groups (for example, different dose levels of the same treatment). Results are examined at the end of the first stage, and one or more of the treatment groups are selected to continue, along with the control group, into the trial's second stage. The final analysis comparing the selected group(s) with the control will use data from the continuing groups from both stages of the trial.

There are three key potential advantages of seamless adaptive designs: a reduction in the duration of the clinical development program, by eliminating the time lag that traditionally occurs between Phase II and III trials; greater efficiency from the use of data from both stages, which might mean that fewer patients are required to obtain the same quality of information; and earlier acquisition of long-term safety data, gathered through continued follow-up of patients from the first stage [27, 31].

There are a number of requirements for successfully implementation of adaptive trial designs [25-28]. Drug responses should be rapidly observable relative to accrual rate. Adaptive trials also necessitate more up-front statistical work to model dose-response curves and to perform simulations – and many simulations are required to find the best combinations of sample size, the randomization ratio between placebo and drug, starting dose and number of doses. This in turn demands efficient programming to develop complex algorithms and programs, and fast computing platforms.

A number of logistical and regulatory actions must be fulfilled to avoid compromising an adaptive trial. To maintain trial integrity, the processes by which interim data are examined and selection decisions are made and implemented must be considered very carefully. First, the actual algorithm for determining the adaptation to implement must be specified in advance. This is usually accomplished by creating a charter for the independent data monitoring committee charged with the responsibility of performing the unblinded interim analysis and communicating as appropriate with the sponsor.

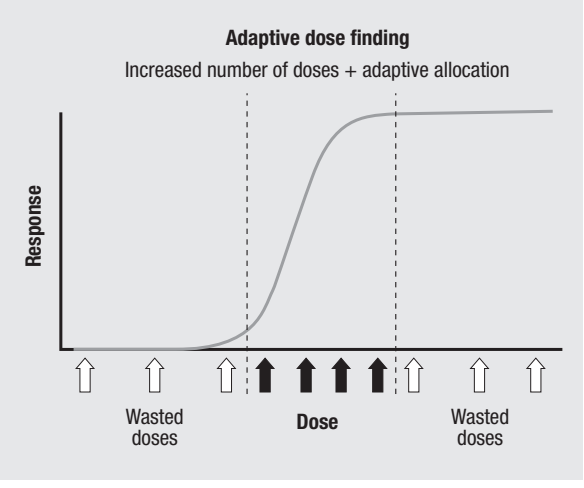

Fig. 3 | *Adaptive dose finding. In a traditional dose-finding trial, selecting a few doses may not adequately represent the dose-response relationship and many patients will be allocated to "non-informative" doses (wasted doses), as shown. In adaptive dose-finding, the strategy is to initially include only a few patients on many doses to explore the dose-response, then to allocate the dose range of interest to more patients. This reduces the allocation of patients to non-informative doses [29, 30]. Reproduced with kind permission from [36].*

SAMPLE SIZE RE-ESTIMATION

Sample size re-estimation (SSR) provides a mechanism for appropriately using the information obtained during a study to inform and adjust the necessary sample size going forward [32, 33]. These methods provide the flexibility to either increase or decrease the sample size at an interim point in the trial. This is important in cases in which there is uncertainty about between-subject variance in the response or uncertainty about the clinically meaningful effect size at which to power the trial. This process increases confidence that an appropriate sample size has been chosen to answer the primary study questions.

SSR usually involves the choice of a suitable initial sample size, including one or more interim analyses at which the sample size will be re-assessed [32]. There are two distinct strategies – the group sequential strategy and the adaptive SSR strategy – for

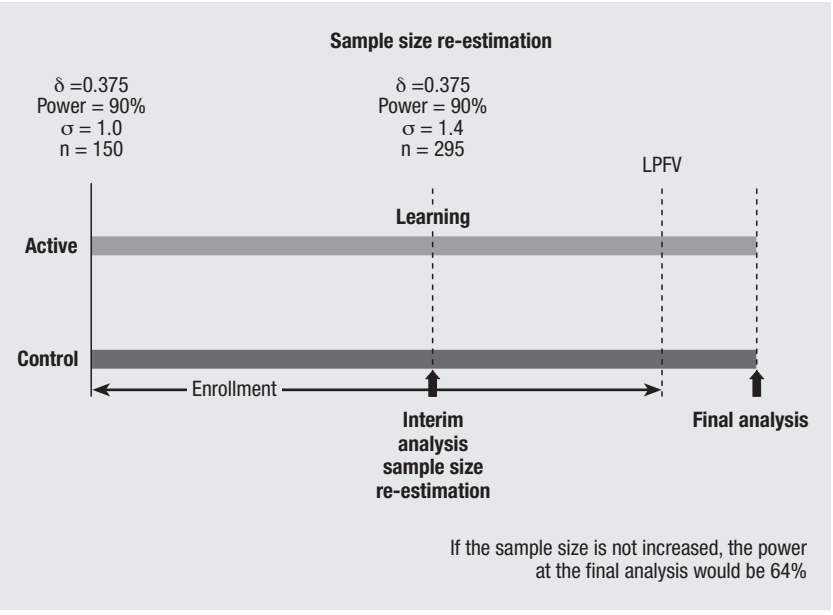

Fig. 4 | *Re-estimating sample size while maintaining statistical power. Hypothetical example of a study in which sample size re-estimation due to uncertainty about δ led to increase in sample size to ensure 90% power was maintained. At the beginning of the trial, the planned sample size was estimated at 150 patients based on a standard deviation of 1.0. At the interim analysis, the actual standard deviation was 1.4. Even though the effect size was as originally predicted, an increase in sample size to 295 patients would be required to maintain 90% power. Without the sample size re-estimation, the power at the final analysis would only be 64% and there would be much greater risk of a failed trial. LPFV: last patient first visit. Reproduced with kind permission from [36].*

choosing the initial sample size, and then altering it on the basis of data obtained at various interim analysis time points. The group sequential strategy, which is also an adaptive design, begins with a large up-front sample size commitment and cuts back if the accruing data suggest that the large sample size is not needed. The adaptive SSR strategy proceeds in the opposite direction, starting out with a smaller initial sample size commitment but with the option to increase it should the accruing data suggest that such an increase is warranted [32-35].

These methods apply equally to situations of unknown effect size δ or standard deviation σ (between subject variability). An illustrative example for unknown σ is shown in *Figure 4*. There are two ways to obtain the new sample size in the situation of unknown σ: blinded and unblinded. In the instance of blinded sample size re-estimation, the sponsor uses pooled data to estimate σ. This is permitted with no penalty to the analysis criteria (that is, alpha, or the probability of Type I (false positive) error). For unblinded sample size re-estimation, the sponsor sets up a mechanism (possibly with the DMC) whereby the SSR is based on an unblinded estimate of variability at the interim analysis. Sample size may be altered one or more times, but the maximum statistical information must be pre-specified.

MOVING FORWARD WITH INNOVATIVE CLINICAL TRIAL DESIGNS

Because they are so flexible, these new trial designs require significant statistical analyses, simulations and logistical considerations to verify their operating characteristics, and therefore tend to require more time for the planning and protocol development phase. Regulatory agencies and institutional review boards also need to approve the design format for interim analysis, and these discussions can sometimes take considerable time. Maximizing the use of all potential prior information requires greater collaboration across functional silos in organizations to avoid compartmentalization of data, and lack of common data standards may prevent the optimal integration of disparate sources of data. These problems are compounded by competitive hurdles to sharing what is considered proprietary information about novel therapies that may prevent the exchange of data. Overcoming internal resistance and aversion to change also represents a major hurdle for incorporating the prospective use of novel trial designs and methodologies, and modelling and simulation, into clinical development programs. Greater awareness of the distinct advantages of innovative designs by regulators and sponsors are crucial to increasing the adoption of these modern tools.

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Conflict of interest statement

The authors are employees of Novartis Pharma AG.

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