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Systems Pharmacology, Pharmacogenetics, and Clinical Trial Design in Network Medicine

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We are at an interesting crossroad in biomedical research. Unmet needs exist in all aspects of medicine. Despite substantial expenditures in research and development of new therapeutics (drugs, devices, biologics), especially over the last two decades, a disturbing minority of investment results in products that successfully pass through a prescribed sequence of hurdles and are approved for addition to the therapeutic armamentarium [1, 2]. For example, estimates of the costs for bringing a new drug through the process of discovery, clinical trials, and FDA approval are between $800 million and $1 billion [3, 4] (Figure 1). Key components of the cost are late-stage failures and expenditures related to Phase II and Phase III clinical trials. The harsh realities of the current system are that ~ 85% of drug therapies fail in clinical trials, that it takes about 10 years to shepherd a new molecular entity through the system successfully, and that only ~25-30 new molecular entities are approved on average per year in the U.S. [2, 5].

The current approach to drug discovery -- using a brute force, sophisticated computationally heavy methodology, centering around high-throughput *in vitro* screening of chemical entities directed at a well-defined molecular target (protein) to find compounds that become lead molecules -- is inefficient [6]. It also does not take full advantage of evolving concepts that the majority of human diseases are the result of a genetic predisposition, random tissue insults, the normal aging process, or some combination of these factors all conspiring through functional molecular networks to yield pathophenotypes [7]. New strategies for target discovery, identification, and validation have been proposed, but continue to focus on singular drug targets [1, 8, 9]. The advent of systems biology, which synthesizes data obtained from individual reductionist perspectives and focuses on construction of integrated, holistic models of determinants of biological responses, offers an exciting opportunity by which to develop new concepts of disease and to identify potential therapeutic targets [10, 11]. The construction of molecular disease networks; the study of their static and dynamic properties; the recognition that drugs do not simply affect a specific molecular target, but perturb the entire disease network; and the use of biomarkers derived from knowledge of the links among these network elements that can be used to predict disease risk and therapeutic response rationally all comprise the basic tenets of the newly described field of network medicine [12]. Similarly, the application of systems biology principles to drug discovery defines the field of systems pharmacology, and offers a rational, holistic approach to the identification of novel, effective drugs that can modulate a key cellular or organismic pathophenotype [13, 14]. In this paradigm, drug target(s) are chosen based on their effects on the networked system response within which it operates, rather than simply on the presence of a biological variant of that target.

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Systems Pharmacology and Pharmacogenetics

To understand the role of systems biology in clinical trials, we must first briefly review the basic tenets of contemporary pharmacogenomics and its relationship to systems pharmacology. Pharmacogenomics is the search for variation in the human genome that predicts human response to drugs. Many pharmacological studies demonstrate that there is substantial between-person variation in response to an individual medication or class of medication [15-17]. Conversely, it is also well known that the within-person response to these same medications is remarkably predictable. This variation in within- and between-person response to drugs has two major causes. The first cause is behavioral, as individuals vary dramatically in their adherence to taking prescribed medications. It is estimated that between 30%-70% of patients either do not fill the prescriptions given them by their physician, or they fill the prescription, but do not take their medication as prescribed, even if it is essential to their health and survival [18]. In addition to age, underlying disease mechanism, and sex, another major cause for the striking between-person variation in drug response is genetic polymorphism. Among patients who take their medications regularly, a significant percentage actually do not respond in the expected way to the drug [19].

Discovering the genetic variants that determine this between-person variability would allow physicians to provide more personalized treatment for patients and is the ultimate clinical goal of pharmacogenomics. By its very nature, pharmacogenomics is a translational field that is focused on discovering predictors of drug response in humans. The identified genetic variants fall into two broad groups: pharmacokinetic variants, i.e., those variants that are present in drug metabolizing enzymes; and pharmacodynamics variants, i.e., those variants that occur in other genes in critical biochemical pathways which govern how the drug exerts its effects. Early examples of pharmacogenetic analysis (in the pre-genome era) focused on candidate genes that were identified by rational biological mechanism (e.g., warfarin, clopidrogel). Contemporary pharmacogenomics leads naturally to the more inclusive field of systems pharmacology [20] (http://isp.hms.harvard.edu/wordpress/wp-content/uploads/2011/10/NIH-Systems-Pharma-Whitepaper-Sorger-et-al-2011.pdf) An example of the application of systems pharmacology principles to pharmacogenomics is the elucidation of the genes involved in steroid synthesis, degradation, and metabolism as a means by which to explain how genetic variation in these genes influences the dynamic behavior of this pathway and, therefore, influences the between-person response to inhaled corticosteroids in asthmatics. [21, 22]

Since the completion of the human genome project in 2000, there has been an explosion of new results that have advanced the field of genetic/genomics and brought these advances closer to clinical practice. It is important to review how these advances have influenced the field of pharmacogenomics as a prelude to considering their application to clinical trials. The completion of the HapMap project in 2006, in which many of the common single nucleotide polymorphisms (SNPS) in the human genome and their pattern of association (linkage disequilibrium) were identified, ushered in the age of the genome-wide association study (GWAS). Genome-wide association studies utilize 500,000 or 1 million SNPs and relate them to a phenotype of interest. Because a large number of genetic variants are tested for a statistically significant relationship to the disease phenotype, there is much greater likelihood of identifying a spurious association (false discovery) than a real association given the large number of statistical tests that are performed. To guard against this concern, the p-value threshold for genome-wide significance in a GWAS is set quite low by statistical convention (typically $p \leq 5 \times 10^{-8}$) [23, 24]. To date, these studies have been somewhat successful, with 1449 genetic loci identified that affect more than 237 specific phenotypes associated with complex traits (http://www.genome.gov/gwastudies/). [25]

These successes notwithstanding, GWAS alone is not the answer to understanding disease pathobiology in complex traits generally, or in pharmacogenomics specifically. The principal reason for this conclusion is that GWAS design is predicated on too simplistic a view of the underlying pathobiology. For example, these studies usually identify a single genetic variant as being significantly related to a phenotype. Owing to the infrequent sampling of the genome, even with 1 million SNPs scanned, this identified variant is unlikely to be the functional variant; rather, it is likely to be a variant that is correlated with the true functional variant via linkage disequilibrium. For this reason, further functional genetic analysis is needed to find the putative functional variant. More importantly, discovering a novel gene in isolation from a pathway or from its interacting genes is of limited value. The explained phenotypic variation (i.e., effect size) of these GWAS loci is small because they fail to take into account a key feature of functional genetics, viz., genes determine phenotype not in isolation but by interacting with other genes (epistasis) [26]. What evolutionarily distinguishes different organisms is less the number of genes they have and more the ratio of noncoding to coding variation in the genome; insofar as the noncoding regions of the genome control gene expression and interaction (via common promoter elements or common microRNAs, for example), these observations support the notion that epistasis is an important determinant of complex phenotype, especially in higher organisms. Current GWAS analysis simply does not take this level of genomic complexity into account.

While these criticisms apply to all GWAS-based studies, there are some specific issues that pertain to pharmacogenomics. First, most genetic association studies in pharmacogenomics have been applied to clinical trials data because these studies have both higher quality drug response phenotype data and are also likely to avoid the problem of medication non-adherence. While these features are clear advantages, one of the disadvantages of this approach is the relatively small size of most clinical trials. Most of the studies in pharmacogenomics are of sample sizes of 2,000 or less, while nonpharmacogenomic GWASs are moving in the direction of trials of 30-100,000 subjects. Clearly if genomics is to be successfully applied to pharmacogenomics, there must be other, novel methodologies that should be utilized in studies owing to these sample size limitations. Fortunately, such approaches are available, and will be reviewed after we review the set of known clinically actionable pharmacogenomic variants.

Pharmacogenomic Variants and Clinical Trials

There are now over 50 pharmacogenetic associations cited in FDA-approved drug labels. Most of the existing clinically actionable pharmacogenomic variants described in the literature have been discovered by GWAS combined with knowledge of the biochemistry of the pathway within which the variant operates. Only a few variants have been identified by candidate gene approaches. As a result of pharmacogenomic trials, the FDA currently requires genetic testing for four drugs: cetuximab (EGRF target), trastuzumab (HER2/Neu target), maraviroc (CCR5 target), and dasatinib (bcr-abl target). Table 2 describes a set of additional actionable pharmacogenomic variants for which the FDA recommends, but does not require, clinical genotype testing.

Although the Pharmacogenomics Research Network (PGRN) is working on developing guidelines for the interpretation of these pharmacogenomic variant tests in clinical practice [27], the reality is that of the seven FDA recommended tests in Table 2, the only test that is routinely used in clinical practice is the HLA-B*5701 variant, which predicts the response to the anti-retroviral drug, abacavir. Of note, this is the only variant that has been validated by a randomized, controlled trial. Clearly, for improved penetration of pharmacogenomics testing into clinical practice, there will need to be clinical trials of either single variants or groups of variants that predict clinical phenotypes.

Future Iterations of Systems Pharmacology

Because pharmacogenomics GWAS are of small sample size and have limited practical possibilities for replication, and because conventional GWAS analysis largely ignores both the functional consequences of GWAS loci and their epistatic interactions, there remains a significant opportunity to apply novel genomic methods via systems pharmacology strategies to genomic discovery. One approach is to integrate sources of genome variation beyond SNPs. For example, methylation marks, transcript abundance, and microRNA profiles can be integrated together with SNP results from GWAS to explain better genome complexity as it may relate to pathophenotype and drug treatment response. An alternate approach is to take clinically relevant cells (liver, kidney, blood) from clinical trial participants, treat those cultured cells with the relevant drug from the clinical trial, and determine transcript abundance in the cell as a function of drug treatment response. These data can then be integrated with GWAS data from the trial to perform a regression of SNP on transcript abundance in order to identify *cis*-acting regulatory variants that can be utilized for pathway construction or network analysis. One can then link these pathways or networks to known pathobiological mechanisms and rational, pathway-based (rather than target-based) therapeutic intervention. This latter approach is illustrated in Figure 3 [28]. Induced pluripotent stem cell technology could make this approach even more powerful by allowing one to assess multiple cell types from the same individual. This strategy would afford the identification of pathways relevant to any systems pharmacology question of interest, such as the effect of a drug on an interacting network of genes or proteins; or those genes or gene products that determine drug levels, or between-person variation to drug levels; or those genes or gene products that are critical for predicting drug treatment response.

Integrating Systems Pharmacology into Clinical Trial Design

Taking a systems or pathway approach to pharmacology in general would address many of the outstanding bottlenecks in drug discovery at the present time. First, a systems approach would allow the integration of the new pathway information generated from the two forms of integrative genomics studies described above and in Figure 3 in order to identify new drug targets or targeted pathways. Second, a systems approach would afford a better understanding of the bases for between-person variation in drug levels and drug response. Third, and perhaps most important, a systems approach would lead to the development of predictive epistatic tests that could be used clinically to predict both adverse events and response to medications.

With respect to these issues in drug development, consider how a systems biology and network medicine approach would have altered the discovery, and contemporary use of statins. Akira Endo focusing on a molecular/target approach screened thousands of fungal extracts and identified the class of HMG CoA reductase inhibitors referred to as statins. [29] Despite the elegant discoveries by Brown and Goldstein regarding the biosynthesis of cholesterol and the importance of LDL receptors, there was limited enthusiasm for commercial development of statins. [29]. This response of the biomedical community stemmed from fears of affecting adversely the structure of cell membranes and unanticipated resulting toxicities. [29]. Eventually, large-scale trials demonstrated the benefits of statins in reducing LDL cholesterol and atherosclerosis-related ischemic events. (Cholesterol Treatment Trialists' Collaboration *Lancet* 376: 1670, 2010) [30]; however, despite the dramatic success of statins, the problem of muscle toxicity continues to plague their use. Nearly two decades since the first large-scale trial that showed the benefits of statins on clinical events, we are left with only theories regarding the mechanism of muscle toxicity from statins. Possibilities include an increase in calcium influx from depletion of intracellular cholesterol, inhibition of a number of metabolic and signal transduction

pathways from a reduction in mevalonic acid, reduction in ubiquinone concentrations, and enhanced apoptosis. [31-33]. More recently, using a systems biology strategy (bioinformatics analysis of whole genome expression profiling of muscle specimens and lipidomics analysis of plasma specimens), Laaksonen and colleagues demonstrated effects of high dose simvastatin on non hepatic tissues as well as a different profile of the effects of atorvastatin on such tissues. [33]. They argue that further understanding of the impact of their lipidomics findings has the potential to lead to individualized drug and dose selection for management of elevated LDL cholesterol [33]. The complexity of the analyses involved is underscored by the report of Buettner and colleagues of the polymorphisms in the gene for atrogin-1, that as a result of this systems-based analysis, has now been implicated in muscle atrophy and is a candidate for one of the mediators of statin-induced muscle toxicity. [32]

Another example of the potential benefits of a network medicine approach to drug development is that of drug combination therapies. In the classic view of drug combinations, one conceives of three interaction types: additive, synergistic, or antagonistic. [34] However, the classical list of interactions is an oversimplification and does not account for the variation in interactions that may occur with different doses. [34] For example, using the concept of isobolograms and response surfaces it is possible to summarize drug interactions when the targets of the drugs are in series in a single pathway or are in parallel pathways. [34-36] Cokol and colleagues, in exploring the concept of synergistic drug pairs, found many drug pairs act by targeting the products of genes that are in parallel pathways [37]; however, using a network analysis, they also identified unexpected synergistic drug pairs that they referred to as “promiscuous synergergizers.” Thus, expansion of the catalog of drug interactions using a network medicine approach, incorporating pharmacogenomics and computational biology, has the potential for optimizing pharmacotherapeutics in the future. [35]

Recognizing the unmet medical needs in drug development and the potential implications of new fields of investigation such as genomics, proteomics, metabolomics, pharmacogenomics, and systems pharmacology, the FDA introduced a Critical Path Initiative in 2004 to drive innovation in the scientific processes by which medical products are developed, evaluated, and manufactured [38]. On the list of Critical Path Opportunities are the concepts of streamlining clinical trials by using information to enrich the trial with subjects having a higher likelihood of response and adapting an ongoing trial in a manner that is responsive to emerging data. [39] The information gleaned from these –omics data sets and their systems-based analysis, coupled with careful clinical phenotyping, represents a rich basis for rational identification of patients likeliest to respond to a drug. Adaptations to clinical trials is not a new concept and has been applied in classically designed trials built on a frequentist structure for some time, especially in the cancer therapy field. The availability of computer modeling, new statistical approaches to analyzing data, the complexity and data-richness of the nascent field of systems pharmacology, and the desire to increase the efficiency of drug development have fueled interest in adaptive clinical trial designs [40]. The complex interplay of statistical and operational issues involved in adaptive designs presents new challenges and has led several regulatory bodies to issue guidance documents for investigators [11, 41].

Conceptual Framework for Adaptations to Clinical Trials

Consider the basic structure of a clinical trial as shown on the right side of Figure 4a. Investigators first establish enrollment criteria for entry into the trial and randomize patients to the regimens being tested. In this example, Treatment A is the control arm and can either be placebo or active therapy (active control), and Treatment B is the test therapy. Although only one arm for Treatment B is shown in the diagram, there may be multiple arms if dose-

ranging is part of the experimental design. Based on the prespecified hypothesis for the trial, the treatments are compared with respect to the development of the primary endpoint, which is ascertained after a period of followup. In a static design, the sample size (established by conventional frequentist methodology) is set prior to enrollment, and the trial continues to completion without modification (Figure 4a). This simple trial structure, although operationally inflexible, tests the hypothesis under consideration, and is familiar to regulatory authorities who have great interest in the safety data such trials provide in the confirmatory phase of drug development (vide infra).

By its very nature, a clinical trial, such as the one shown in Figure 4, is associated with uncertainty about the relative efficacy and safety of the treatment arms; hence, the ethical basis for such research as conveyed in the term, equipoise [42]. At the design stage of the trial, there is a limited amount of information known about the response to exposure to the test intervention. In statistical terms, there may be sparse information about the parameters needed to describe adequately the treatment effect of the test intervention [11]. It is generally appreciated that there will be variation in response to the test intervention in the cohort of patients who fulfill the enrollment criteria. The cohort of patients entering the trial is a subset of the universe of patients with the disease state under study, and their responses may or may not be a fair representation of the distribution of responses of all patients with the disease of interest if they were to receive the test intervention. The concept of adapting an ongoing trial to evolving information about the profile of patients expected to have a more robust, positive response to the test therapy is appealing to sponsors and investigators as it enhances the likelihood of success of the trial.

It has been proposed that adaptations to clinical trials make biological sense, since information from highly dynamic fields, such as pharmacogenomics and functional genetics, is likely to become available during the course of enrollment and followup in the trial (Figure 4b). It has been argued that permitting adaptations to clinical trials offers greater flexibility than a conventional trial with a fixed design (frequentist approach), is a potential solution to the “pipeline problem,” and is likely to reduce the cost of drug development [8, 9]. Combined with new systems pharmacology-based approaches to identification of targets or pathways for testing and pharmacogenomic predictors of drug response, adaptations to clinical trials may accelerate the delivery of new treatments to fulfill unmet medical needs [1,43-45].

Before considering the details of adaptive designs of clinical trials, it is useful to review the standard approach to clinical development of a new molecular entity. It should be emphasized that the concept of adaptive design is a descendant of the original learn-and-confirm approach to drug development introduced by Sheiner. [46] He conceived of a therapeutic response surface that related patient factors, the dose regimen, and the net benefit (efficacy/toxicity) of the regimen. In the learning phase, the population studied is heterogeneous, pharmacokinetics is a major focus, and the analysis emphasizes modeling in the as-treated population. [46] The confirmatory phase studies a more homogeneous population (as suggested from the learning phase), clinical outcomes are the main focus (efficacy and safety), and the analysis uses the as –assigned (intention-to-treat) approach. [46] In his original conception of the patient axis of the therapeutic response surface, Sheiner collapsed a large multidimensional array of information into an unidimensional construct. The advances of pharmacogenomics and computational biology in the framework of a network medicine approach now offer the potential for representing the complexity of the inter-individual variation in a more informative fashion.

The modern day version of the two broad phases of drug development are illustrated in Figure 6. The exploratory phase involves modeling disease phenotype by integrating data

using a systems approach. [47] Critical goals of the first-in-human and proof-of-concept investigations (Phase I studies in normal volunteers) during the exploratory phase are designed to identify any signals of concern regarding safety, and propose dose regimens (dosing, timing) to be taken forward to the confirmatory phase (Figure 1). In the confirmatory phase, patients with the disease of interest are studied to provide further information on dose-ranging (Phase II) and to establish definitively the benefit-to-risk ratio for the new drug (Phase III) (Figure 1).

Adaptations to Clinical Trials

Adaptations to the design and conduct of the trial can generally occur at the three major levels shown by the arrows in Figure 4b. Depending on the circumstances, adaptations may occur in several elements of the individual arrows and may also occur at more than one of the levels depicted. The types of adaptations from the lists shown in Figure 4b may be different during the exploratory and confirmatory stages of drug development [11]. Contemporary tools that are frequently used to drive the adaptation include modeling and simulation. Bayesian methodology is used with increasing frequency to update predictive probabilities and the pertinent statistical models of the trial [48].

The source of information that leads to the adaptation may vary (Figures 4c and 4d). According to regulatory guidance documents, when the information flows from a source external to the trial and provokes an adaptation, it is referred to as a *reactive revision* (Figure 4c) [11]. When the investigators prospectively plan to adapt the trial based on interim data internal to the trial, the term *adaptive design* is used (Figure 4d) . Unplanned findings that arise upon review of interim data are also important and are anticipated to occur more frequently as fields such as systems biology and systems pharmacology mature (Figure 4d). Such unplanned findings may provoke an adaptation to the trial, as well, which is less problematic during the exploratory phase than during the confirmatory phase of drug development.

From a regulatory perspective, there is less concern about adaptations during the exploratory phase of drug development than the confirmatory phase as it is anticipated in the former that the type I error rate is not likely to be as rigorously controlled as in the latter. Regulatory authorities will scrutinize adaptations to trials performed during the late stages of the confirmatory phase, where adequate design and control are paramount [11, 41]. Regulatory authorities wish to be certain such adaptations protect the validity (e.g., studywide Type I error rate, consistency between stages of the trial before and after the adaptation) and integrity (e.g., minimization of operational bias, accumulation of information that will be informative to the clinical community) of the trial [11, 41]. Regulatory authorities have also highlighted statistical concerns when pharmacogenomics-based analysis are submitted based on convenience samples from a confirmatory trial to identify patients who appear to be genomically favorably disposed to respond to the test therapy. [49]

Examples of Adaptations to Clinical Trials

Exploratory Phase

During this phase, information about response to interventions that interact with the target identified during the discovery phase is limited and the sample size is typically small. Consider the theoretical dose-response curve shown in Figure 7. Given their importance from a regulatory perspective, an important initial goal of dose ranging is to identify the doses having no effect and the maximally tolerated doses. The typical sigmoidal shape yields flat portions of the dose-response curve that are less informative than the steeply

sloped mid-portion of the curve. Administration of such "wasted" doses as may be given at these flat portions of the curve to many subjects is undesirable.

Once the boundaries of the rapidly rising portion of the curve are demarcated, a major goal is to enroll patients along the rapidly rising portion of the dose-response relationship to identify efficiently a dose range for the therapy. An example from the cardiovascular clinical trials literature of antithrombotic therapy for acute myocardial infarction illustrates this principle. During the development of combination reperfusion therapy with reduced dose fibrinolytics plus glycoprotein IIb/IIIa inhibitors, a sequential probability ratio test (SPRT) was used to identify rapidly candidate regimens that held promise for restoring blood flow in a thrombotically occluded coronary artery [50]. The structure of the SPRT centered around historical data showing that ~50% of angiographically evaluable patients achieve full antegrade flow (TIMI grade III flow) with a front-loaded 100 mg alteplase regimen. The TIMI 14 study, which tested abciximab plus varying doses of fibrinolytics as part of the combination reperfusion regimen, was an open label angiographic trial. The prespecified SPRT boundaries that were used to guide the Operations Committee were 30% (H_0) and 50% (H_a) TIMI III flow with types I and II error rates of 0.0001% and 10%, respectively, for the abciximab-alone group, and boundaries of 60% (H_0) and 80% (H_a) TIMI III flow with types I and II error rates of 1% and 2.5%, respectively, for groups in which abciximab was combined with a fibrinolytic agent [50]. It was estimated that 35 to 70 patients per treatment group would provide sufficient information to determine whether a given regimen was likely to be considered a candidate for additional testing. While the adaptive design to dose ranging in trials like TIMI 14 was helpful in identifying candidate regimens, a large confirmatory Phase III study identified a serious safety concern of excessive bleeding [50-52].

Understanding the subtleties of the dose regimen, such as once daily versus twice daily dosing and the need for adjustment for renal failure and drug interactions, is important for indentifying the optimum dose to be tested in a phase 3 confirmatory trial. [53, 54] While pharmacometric information can be gleaned from a phase 3 trial and potentially used to seek approval for a dose not explicitly tested in the pivotal registration trial, it is preferable to have completed the modeling work based on pharmacogenetic and system pharmacology analysis before embarking on a large, costly multicenter trial. [55]

Advances in target discovery, identification, and validation offer the possibility of defining a dose-response in a more refined fashion [1]. An example from dose-ranging studies in the development of novel cancer therapeutics illustrates how adaptive designs may take advantage of molecularly targeted agents [56]. In conventional dose-ranging with cytotoxic cancer agents, a common design is the 3+3 approach to constrain the toxicity rate to ≤33% [56]. The 3+3 design first enters 3 patients at a given dose level. If no patients exhibit dose-limiting toxicity, enrollment at the next higher dose level may occur; if one patient exhibits dose-limiting toxicity, at least 3 more patients are enrolled at that dose. When the rate of dose-limiting toxicity is estimated to be 33%, the next lower dose is identified as the recommended Phase II dose. New molecularly targeted agents are less likely to be cytotoxic, and, it has been argued, more aggressive dose-ranging studies are, therefore, appropriate for the development of such agents. A variety of accelerated dose titration schemes have been proposed that include a rapid initial dose-escalation phase, intrapatient dose-escalation, and statistical analysis of a dose-toxicity model [46, 57]. Another aggressive form of dose escalation is the continual reassessment method that specifies a target level of toxicity, the number of patients per cohort, a mathematical model of dose-toxicity, and formal stopping rules [58]. An example of a continuous reassessment method with Bayesian updating of the probability of dose-limiting toxicity after each patient is assessed at a given dose is shown in Figure 8.

At the interface between the exploratory and confirmatory phases of drug development, one finds Phase II trials (often divided into Phase IIa that focuses predominantly on dose-ranging, and Phase IIb that continues to provide dose-ranging data but also focuses on providing more efficacy data) (Figure 1). The desire to increase efficiency of drug development has led to the concept of combining an adaptively designed Phase II trial with a Phase III trial in a seamless fashion [59-62]. An example from the pulmonary medicine literature illustrates the advantages and challenges of this approach. The long-acting beta-agonist, indacaterol, was studied in patients with chronic obstructive pulmonary disease using an adaptive design dose-ranging Phase IIb study comparing the efficacy of 75, 150, 300, and 600 mcg doses versus placebo over 2 weeks with respect to the forced expiratory volume in one second (FEV_1). Prespecified efficacy criteria were used and the 150 and 300 mcg doses were taken forward in a Phase III trial [63]. Review of the new drug application by the FDA raised concerns that, in fact, all doses of indacaterol were superior to placebo and had a similar effect size [64]. Owing to concerns about toxicity of long-acting beta-agonists with chronic use (especially in asthmatic patients), additional dose-ranging and safety analyses were requested by the FDA, ultimately leading to the approval of the 75 mcg dose for use [64]. This example illustrates the challenge of accelerating drug development using prespecified efficacy criteria while ensuring that safety concerns have been adequately addressed.

Another example of an adaptively-designed Phase II trial illustrates how efficacy and safety assessments may be incorporated in decision-making about dose selection. The selective phosphodiesterase 3 (PDE 3) inhibitor, K-134, was identified in Phase I studies to have vasodilatory effects and more pronounced antiplatelet effects than cilostazol [65]. A double-blind trial of 3 doses of K-134 (25, 50, and 100 mg twice daily) was designed to compare it with placebo or cilostazol (100 mg twice daily) in patients with stable claudication [65]. The goal of the adaptive design was to eliminate one of the K-134 regimens quickly if adverse effects or intolerability occurred at an unacceptable rate. The safety endpoints, which were designed with cutoffs of 20% of the population exhibiting them, were resting tachycardia (HR >120 bpm) and ischemia on treadmill testing; the tolerability endpoint (40% population cutpoint) was discontinuation of the study drug for any reason. Interim analyses were designed with 80% two-tailed confidence intervals for each endpoint based on logistic dose-response models. Monte Carlo simulations were used to establish the 80% confidence interval as a reasonable approach [65]. The 25 mg dose was ultimately dropped on recommendation from the Data Monitoring Committee, and the investigators estimated that the design described above prevented approximately 43 subjects from being assigned to a rejected dose had a conventional fixed design had been used [65].

Another dimension to the exploratory phase that is now increasingly possible is identifying a profile of patients who are much more likely to have a beneficial response on the basis of biomarker measurements. This concept is, perhaps, best exemplified in the field of cancer therapeutics where the complex molecular aspects of tumor biology necessitate the development of targeted molecular agents. A striking example is the development of the B-RAF inhibitor, PLX4032, in patients with malignant melanoma harboring the V600E B-RAF mutation [66]. As another example, the I-SPY 2 Phase II trial of neo-adjuvant chemotherapy for women with large primary cancers of the breast (>3.0 cm) is stratifying subjects based on biomarker assessment of hormone receptor status (ER, PR), HER2 status, and the MammaPrint score [67]. Fourteen biomarker profiles of interest have been identified, and subjects are assigned to a particular neoadjuvant regimen based on the regimen's updated Bayesian predictive probability of success in a Phase III confirmatory trial. New candidate drugs may be introduced during the course of the trial, for which reason bioinformatics support is being used to integrate genomics, proteomics, pathology, and imaging [67] in the planned trial adaptations.

Confirmatory Phase

The process of adapting a clinical trial to evolving data has been applied during the confirmatory phase of therapeutic development, as well. A number of statistical papers have appeared providing tools for investigators who wish to use an adaptive design in a confirmatory trial [60, 61, 68, 69]. Various classification schemes have been proposed, such as whether the adaptation affects the trial conduct or the statistical procedures; or whether the adaptation is planned prospectively, occurs in an ad hoc fashion concurrent with the ongoing trial, or is a retrospective maneuver implemented prior to database lock and unblinding of the treatment codes [62, 70, 71]. Given the complexity of the type and number of adaptations that may be implemented by investigators, we developed the classification scheme shown in Figure 4b, which also depicts the regulatory perspective on the sources of information that drive an adaptation (Figures 4c and 4d) [40]. General concerns about adaptations to confirmatory trials include the need to protect the study-wide type I alpha error and prevention of operational biases that may jeopardize the integrity of the study [11, 41, 62, 71-74].

There are three statistical penalties that occur during the process of adaptation [75].

1. By focusing on optimizing the chances of a successful result with respect to the primary endpoint, adaptations to the trial may limit the amount of information related to other endpoints or research questions. The extent of information that becomes available to the clinical community may, thus, be limited.
2. Efforts to control the overall type I error limit the efficient use of information compared with a fixed design trial.
3. Adaptations to the trial frequently alter the sampling distributions used in the summary statistics, which may present inferential challenges for readers of the trial results.

Practical issues that must be considered when designing a confirmatory trial with an adaptive design include the requirement that the information driving the adaptation must be available in a reasonable timeframe after randomization to implement the adaptation (i.e., adaptive design may not be practical in long-term studies), the additional complexity of preparing study drug kits when estimates of supplies cannot be projected accurately at the start of the study, the need to analyze “overrunning” patients who are enrolled in the trial after the cutoff for data collection for an interim analysis, and the logistical requirements for preventing release of interim information to trial personnel (e.g., risk of operational bias by “reverse engineering” of the announcement of the adaptation to estimate the therapeutic response in the treatment groups) [11, 41, 72-74]. Cook and DeMets point out that the decision to implement an adaptation is a difficult one for a Data Monitoring Committee once it has seen unblinded interim outcome data [75]. This challenge necessitates consideration of separating the group with decision-making authority about adaptation from the Data Monitoring Committee, and keeping both groups at arm’s length from the investigators and sponsors [73, 75]. Consider the complexities involved in an event driven trial with three arms: a control arm and a high and low dose arm of the experimental therapy. [54] Since both of the experimental arms are to be compared with the control arm, it is not logistically possible for the Data Monitoring Committee to recommend stopping one of the experimental arms and allowing the other to continue without risking unblinding the investigators. By reverse engineering the calculations from the aggregate number of events, the investigators could make an inference about the treatment effects in the arm that is stopped compared with the one that is continued. To protect the integrity of the trial, it would need to be continued until the requisite number of events had been accrued for each comparison –low dose versus control and high dose versus control.

If an adaptive design is used in a confirmatory trial, prospective consultation with regulatory authorities is recommended along with clearly prespecified operating procedures [11, 41]. Some adaptations to confirmatory trials are well understood by regulatory authorities and are discussed below.

1. Adaptations to Enrollment Criteria and Sample Size (Figure 4c)

When designing the inclusion and exclusion criteria of a confirmatory trial, investigators construct a profile of patients that is believed to reflect their responsiveness to the test intervention's mechanism of action and that maximizes demonstration of a treatment effect. During the course of the trial, screening logs may be reviewed or blinded interim data may be inspected. If the findings suggest that the population being enrolled does not have the anticipated baseline characteristics, the enrollment criteria may be modified to enrich the characteristics of patients enrolled subsequently into the trial toward those with the desired characteristics. Statistical concerns are minimal as long as the treatment allocation remains blinded; however, a potential practical concern may arise regarding interpretation of the study results if there is an important difference in the treatment effect in the trial population enrolled before and after the adaptation [11].

The sample size for the trial may be re-estimated from blinded aggregate data. This approach permits investigators to protect the power of the study by increasing the sample size if they judge that the original assumptions used in planning the trial are inaccurate. When observing a low blinded aggregate event rate, investigators cannot distinguish between a lower event rate in the control group versus a larger treatment effect than anticipated. For example, the CURE investigators increased the sample size of a confirmatory trial of clopidogrel in unstable angina/NSTEMI on the basis of a low aggregate event rate, which had resulted from a larger than anticipated treatment effect [76].

2. Adaptations to Treatments, Allocation Ratio, Data Collection Schedule (Figure 4c)

An adaptive technique that is familiar to investigators and regulatory authorities is the pre-specification of the number and timing of interim analyses where an independent group (Data Monitoring Committee) inspects the accumulating data [11, 41]. Such group sequential designs typically prespecify stopping boundaries that control the type I error rate by controlling the spending of alpha at each interim assessment of the data. Potential decisions that may be made at an interim assessment include termination of the trial because of futility, or overwhelming evidence of efficacy or safety concerns. In a multiarm trial that involves different doses of a therapeutic intervention, an ineffective dose may be discontinued ("drop the loser") while other arms are continued [77]. Alterations to the allocation ratio between the treatment arms based on interim results (responsive-adaptive randomization, "play the winner") are helpful in the exploratory phase of development (Figure 5) but are difficult to implement while still maintaining the validity and integrity of a confirmatory trial [11]. As information becomes available, either from an external source or the ongoing trial, investigators may have a greater understanding of the biology of the disease state and/or the treatment being investigated that drives a decision to modify the data collection schedule. This decision should, of course, be made in a blinded manner without access to the treatment assignments.

3. Adaptations to Primary Endpoint, Analytic Methods, or the Trial Hypothesis. (Figure 4c)

Based on external data regarding the test intervention or a lower than anticipated event rate, investigators may surmise that the treatment effect is likely to be less than expected. This may result in a modification of the primary endpoint, often adding or removing elements of a composite endpoint [11, 41, 78, 79]. Such maneuvers by investigators should be done in a blinded fashion and before database lock. Analytic methods may be altered after a blinded

inspection of the data to account for new information, such as additional covariates, other external data sources, or shifts in methodology, such as parametric versus nonparametric techniques [11]. Active control trials may be designed with a non-inferiority hypothesis using a non-inferiority margin based on historical studies [80]. Investigators should avoid concerns about non-inferiority margins by prespecifying the margins and using a closed testing procedure to test for superiority, conditional on having shown noninferiority [41]. Increases in sample size based on blinded aggregate data may be useful for increasing the power to demonstrate both noninferiority and superiority. Regulatory and clinical concerns arise, however, if an adaptation to enrollment criteria causes the trial population to deviate from the historical reference (i.e., loss of constancy assumption).

Despite the excitement surrounding adaptive clinical trials and the creativity of biostatisticians in helping design them [68, 69, 81], regulatory authorities are cautious about adaptive designs in confirmatory trials [11]. This caution has led some individuals to conclude that adaptive designs have their greatest utility in the exploratory phase of therapeutic development---a realm in which systems biology and systems pharmacology may have its most significant impact (Figure 1) [82].

Conclusions

The rapidly advancing fields of systems pharmacology, pharmacogenetics, and network medicine provide unique insights that can be used to tailor therapies to specific pathophenotypes with optimal efficacy and minimal adverse effects. In order to exploit the implications of these expanding fields, the discipline of clinical trial design must also evolve from static trial designs to designs that accommodate rational adaptation to new knowledge. Fortunately, clinical trial methodologies have met this challenge with evolving statistical and design strategies, leading to a promising future for effective drug assessment for optimal clinical outcomes.

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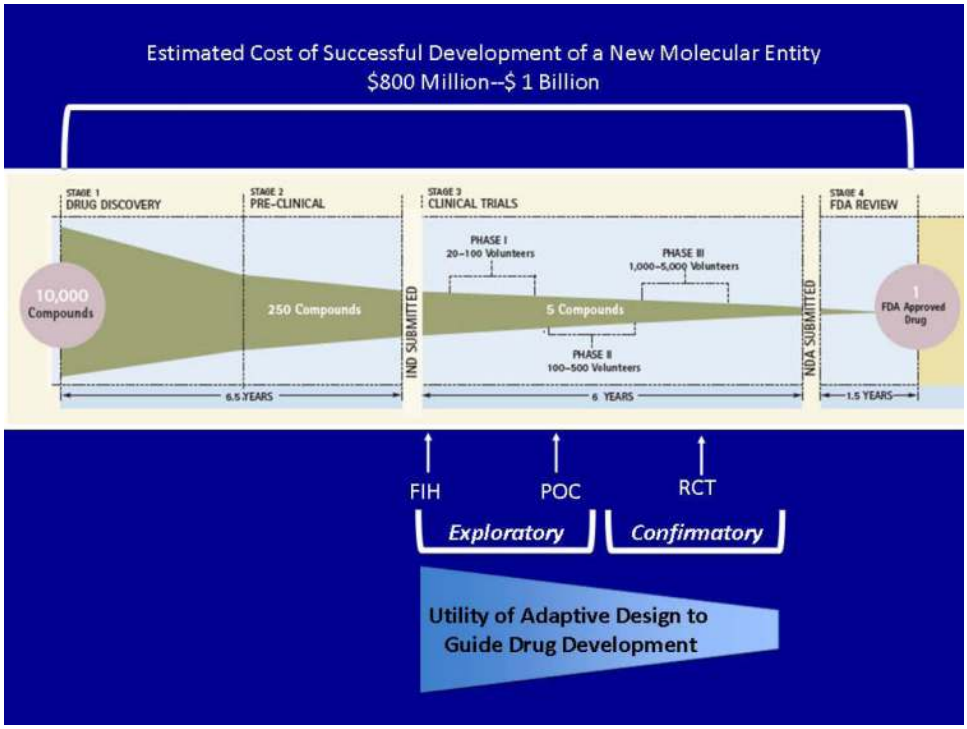


Figure 1. Schematic diagram illustrating the stages and time course of drug development

Once pre-clinical testing is complete, the first-in-human (FIH) and proof-of-concept (POC) studies are performed. These are critical elements of the exploratory phase of drug development, which is followed by the confirmatory phase, characterized by large Phase III, registration-pathway trials. As emphasized at the bottom of the figure, adaptive design has its greatest utility in guiding the exploratory phase of development.

(Modified from Alexander JC, Salazar DE. Modern Drug Discovery and Development. In: Robertson D, Williams GH, eds. Clinical and Translational Science: Principles of Human Research. London: Academic Press; 2009:361-380.)

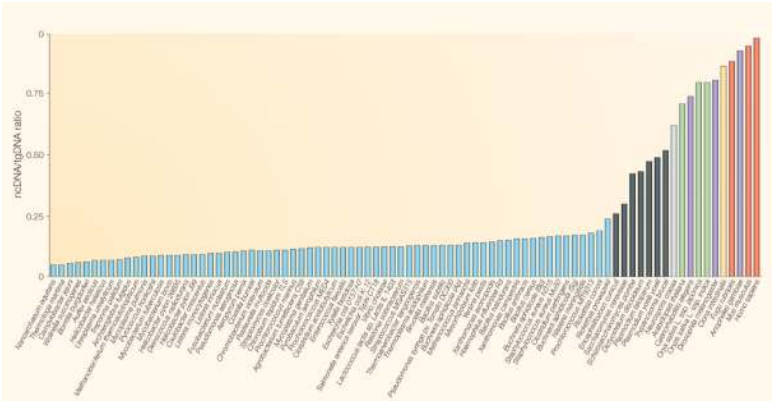


Figure 2. The ratio of non-coding to protein-coding DNA across species
(Reproduced with permission from Mattick, et al., Nat Rev Genet 2004;5:316-323).

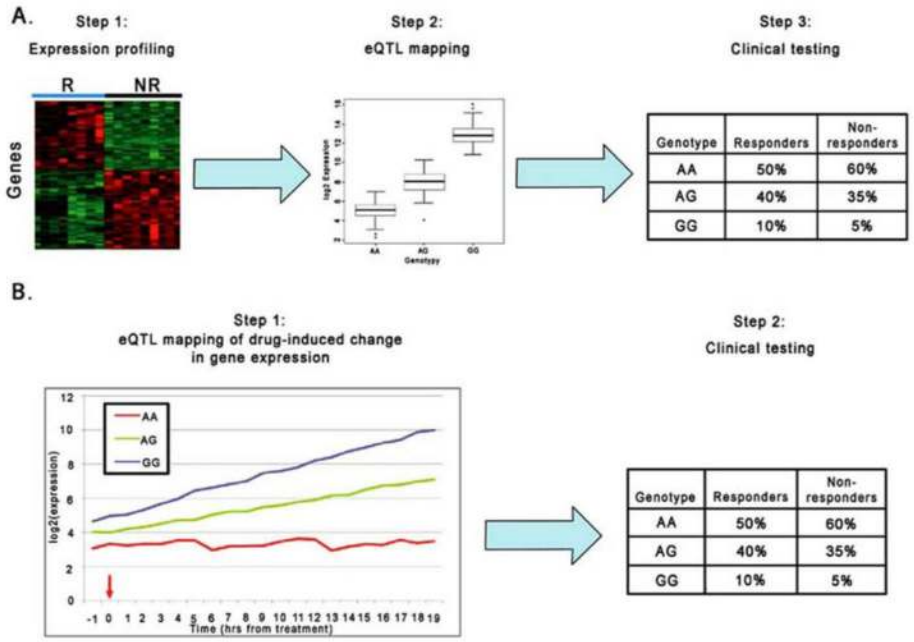
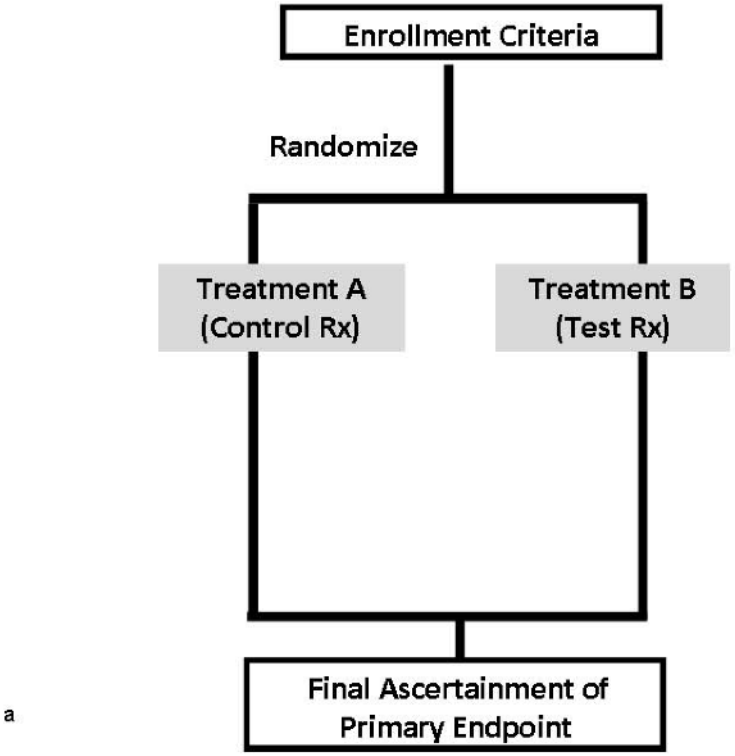


Figure 3. Pharmacogenetic expression quantitative trait loci (eQTL) study designs

Panel A: Sequential design - comparison of microarray expression profiles of responders (R) with non-responders (NR) for identification of pharmacogenetic candidates (Step 1), followed by eQTL mapping of candidate gene expression levels in a larger sample (Step 2). Significant eQTLs are subsequently carried to clinical cohorts for classical pharmacogenetic testing (Step 3).

Panel B: Perturbation design - time-series experiment measuring global gene expression in response to drug administration (arrow), testing for SNP-specific differences in response phenotype (Step 1), which can then be carried forward to clinical testing in Step 2. These designs are not mutually exclusive. (Reproduced with permission from [28].)



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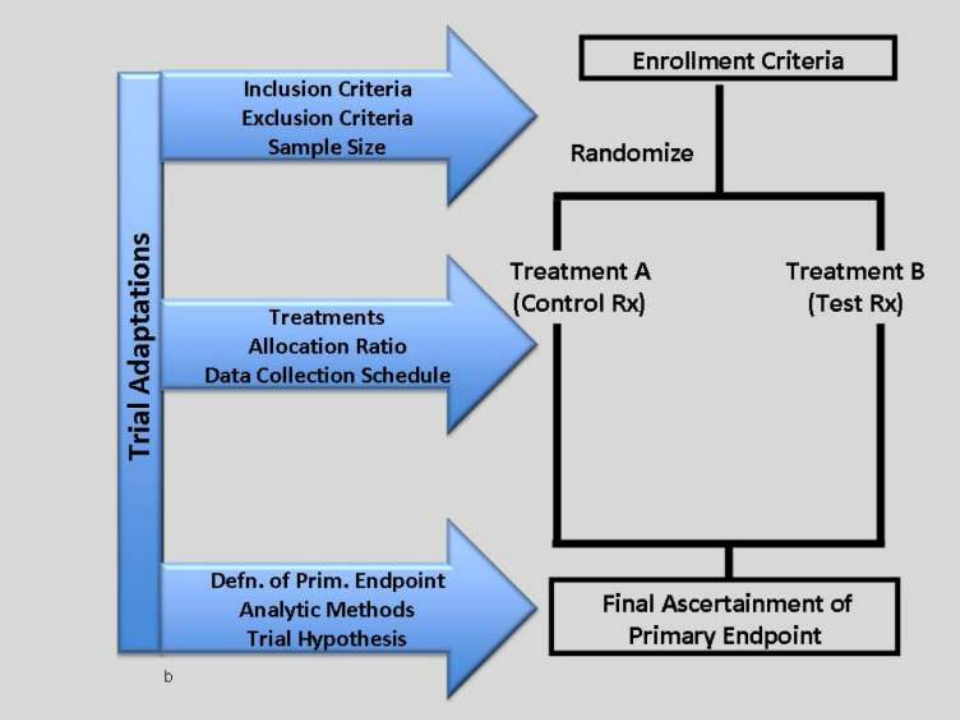

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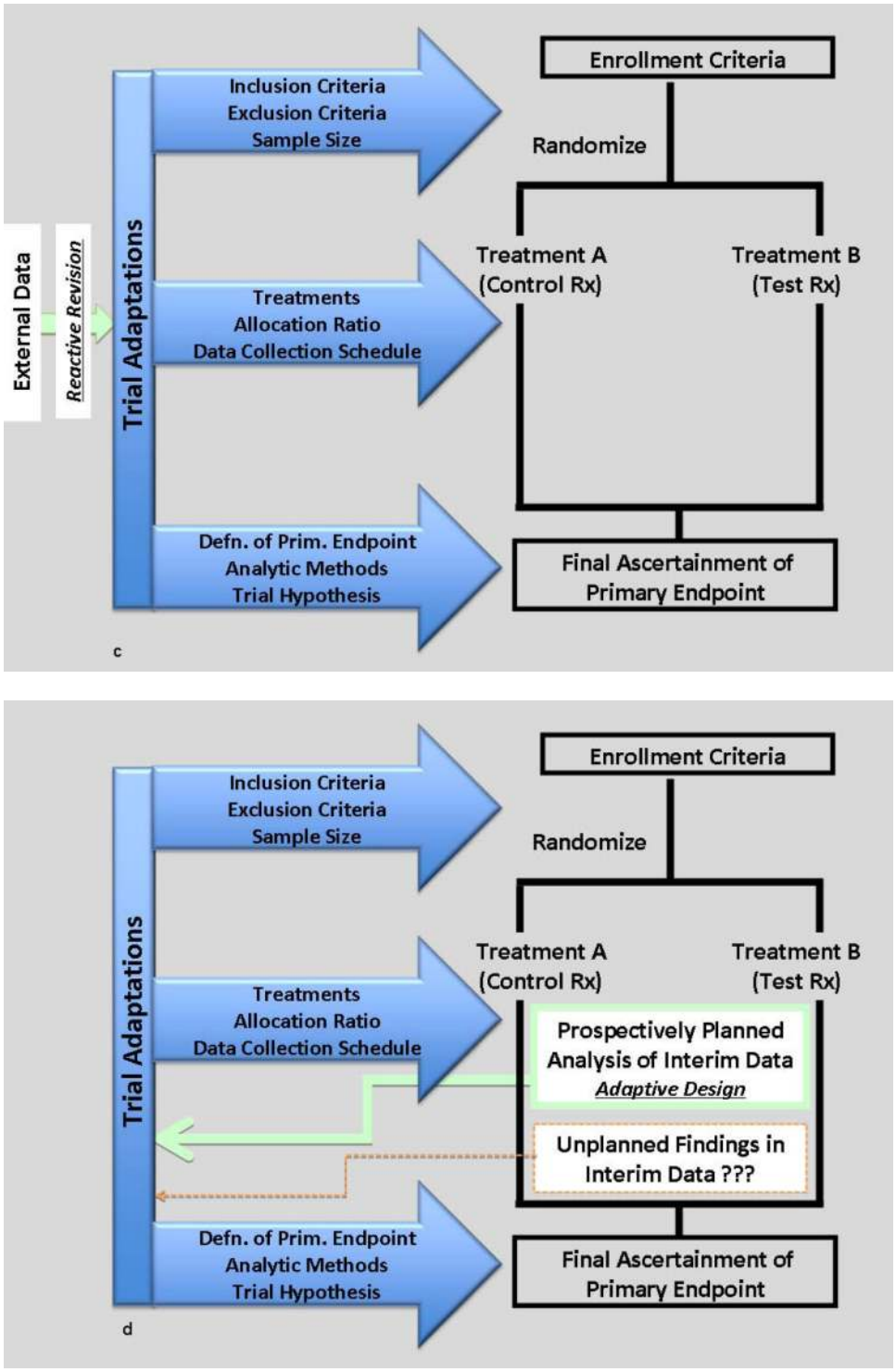

Figure 4. Adaptations to Clinical Trials

A schematic diagram illustrating the basic structure of a clinical trial is shown in Panel A. Adaptations to clinical trials generally occur at the three levels depicted by the blue arrows shown in Panel B. The sources of information that drive a decision to adapt the trial vary and include data from an external source (Panel C), a prospectively planned analysis of interim data from the trial, and unplanned findings arising from an interim analysis (Panel

D). The first two situations are referred to as a reactive revision (Panel C) and an adaptive design (Panel D), respectively.

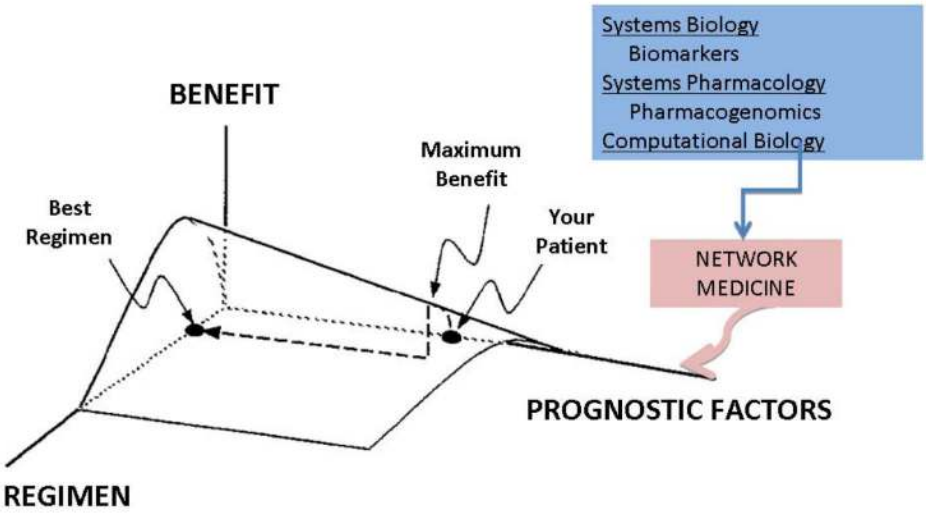

Figure 5. The Learn-and-Confirm approach to drug development

First developed by Sheiner [83], this approach can be adapted to incorporate modern systems principles and network medicine to revise, make rational, and facilitate optimization strategies for drug development.

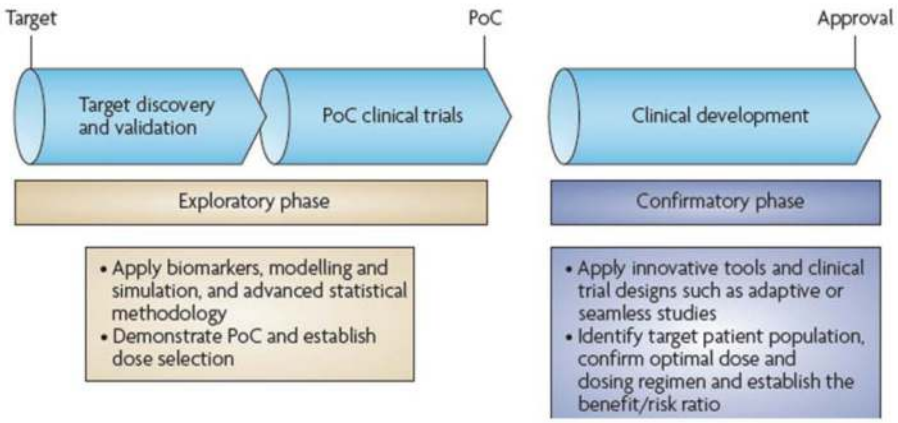

Figure 6. A novel model for clinical development

During the exploratory phase of development, this model uses all available knowledge and tools, including biomarkers, modeling, 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 goal of identifying the target patient population in which the drug is efficacious, establishing the benefit-to-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.

(Reproduced with permission from Orloff J, Douglas F, Pinheiro J, et al. The future of drug development: advancing clinical trial design. *Nature reviews. Drug discovery.* 2009;8:949-957)

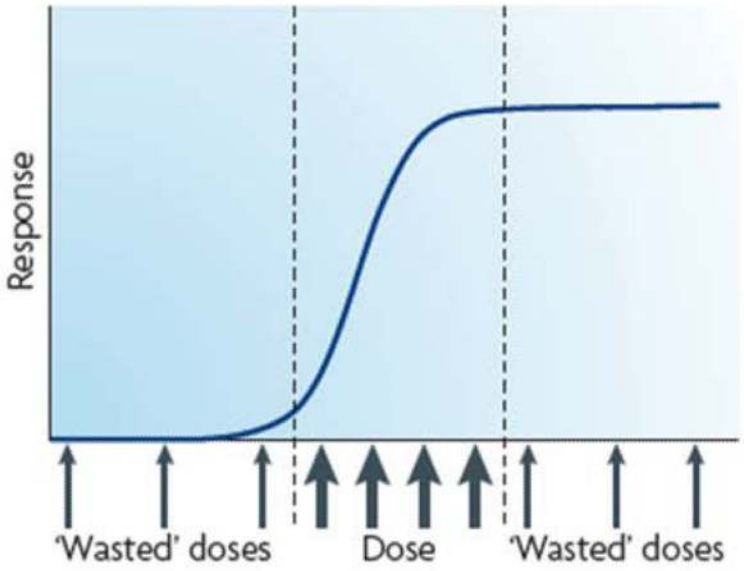

Figure 7. Adaptive Dose-finding Study

In an adaptive dose-finding study, 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 (e.g., variability in parameter estimates). In a traditional dose-finding trial, selecting a few doses may not adequately represent the dose–response relationship, leading many patients to be allocated to 'non-informative' doses (wasted doses), as shown in the figure. In adaptive dose-finding, the strategy is to include initially only a few patients on many doses to explore the dose-response, then to allocate the dose range of interest to a greater number of patients. This strategy reduces the allocation of patients to non-informative doses. Compared with fixed randomization, this approach has the ethical advantage that fewer subjects are assigned doses that are too high or too low; it can also avoid additional, separate trials that might be necessary when fixed dose-finding trials do not adequately define the dose range. Adaptive dose-finding trials also require an infrastructure that allows the rapid communication of responses from trial sites to a central unblinded analysis center and of adaptive dose assignments to the trial sites. Randomization software capable of rapidly computing dynamic allocation of doses to subjects is additionally mandated by adaptive trials because pre-specified randomization lists will not work. In addition, a flexible drug-supply process is required because demand for doses is not fixed in advance, but. Rather. evolves as information on responses at various doses is gathered as the trial progresses.

(Modified with permission from Orloff J, Douglas F, Pinheiro J, et al. The future of drug development: advancing clinical trial design. *Nature reviews. Drug discovery.* 2009;8:949-957)

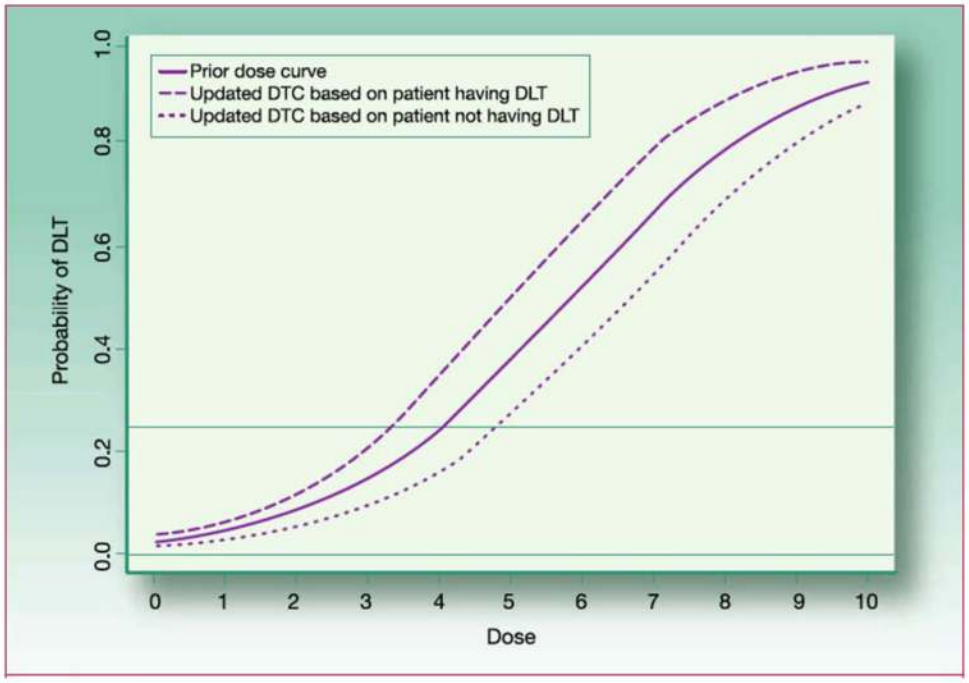

Figure 8. Theoretical Dose–toxicity Curves (DTCs) for continuous reassessment method with one patient per cohort

The solid line shows the prior dose-toxicty curve (DTC) from which the dose for the first patient is selected. With a desired dose limiting toxicity (DLT) rate of 0.25, the dose level for the first patient is level 4. The dashed line shows the estimated DTC after observing the first patient if the first patient experienced a DLT. If the first patient experienced a DLT at level 4, then patient 2 would receive dose level 3. The dotted line shows the estimated DTC if the first patient did not experience at DLT at level 4; patient 2 would receive dose level 5. (Reproduced with permission from Ivy SP, Siu LL, Garrett-Mayer E, Rubinstein L. Approaches to phase 1 clinical trial design focused on safety, efficiency, and selected patient populations: a report from the clinical trial design task force of the national cancer institute investigational drug steering committee. Clinical cancer research : an official journal of the American Association for Cancer Research. 2010;16:1726-1736.)

Table I

Percentage of the Patient Population Not Responding to a Particular Drug or Drug Class

Anti-Depressants	38%
Asthma Medications	40%
Diabetes Drugs	43%
Arthritis Drugs	50%
Lipid Lowering Drugs	50%

Spear BB, Heath-Chiozzi M, Huff J. 2001. Clinical application of pharmacogenetics. Trends in Molecular Medicine 7(5):201-204 [5]

Table II

FDA Approved Pharmacogenetic Tests

Drug	Gene	Variants	Clinical Trial	Use in Clinical Practice
Coumadin (Warfarin)	CYP2C9 VKORC1	*2 *3	No	+/–
Plavix (Clopidogrel)	CYP2C19		In Progress	+/–
Ziagen (Abacavir)	HLA-B *5701	*5701	Yes	++++
Purinethol (GMP)	TPMT		No	+/–
Tabloid (Thioguanine)				
Inman (Azathioprine)				
Camptosar (Irinotecan)	UGTIAC	*28	No	+/–
Carbamazine	HLA-B	*1502	No	+/–