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# REVIEW ARTICLE

## Innovative highlights of clinical drug trial design



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**Clinical trials serve as the gold standard to evaluate the efficacy and safety of tested drugs prior to marketing authorization. Nevertheless, there have been a few challenging issues well noted in traditional clinical trials such as tedious processing duration and escalating high costs among others. To improve the efficiency of clinical studies, a spectrum of expedited clinical trial modes has been designed, and selectively implemented in contemporary drug developing landscape. Herein this article presents an update on the innovated human trial designs that are corroborated through coming up with approval of notable therapeutic compounds for clinical utilization including delivery of several blockbuster products. It is intended to inspire clinical investigators and pharmaceutical development not only timely communicating with the regulatory agencies, but also insightful translating from cutting-edge scientific discoveries. (Translational Research 2020; 224:71–77)**

### INTRODUCTION

The randomized controlled clinical trials (RCTs) of sequential 3 phases have been traditionally regarded as an official paradigm during drug development for decades. While phase I study is to define the tolerability, pharmacokinetics and adverse effects, subsequently phase II and then III studies are to examine the therapeutic efficacy in exploratory and confirmatory manners respectively.<sup>1,2</sup> Although RCTs historically played and are still playing a decisive role in evaluating efficacy and safety of a therapeutic agent prior to the marketing authorization, the implementing practice also came up with several challenges including tedious processing duration, ever-escalating costs and lack of subgroup

differentiation for maximizing clinical benefits.<sup>2,3</sup> To circumvent these problems, the significant advancement in disease biology and clinical pharmacology has inspired emergence of a spectrum of innovated clinical trial designs in contemporary drug developing landscape.<sup>2,3,4</sup>

Overlapping with the essential principles of classic RCTs, these recently emerged clinical studying models are characterized by an impressive list of additional strengths such as improved time and cost effectiveness among others.<sup>3</sup> Based upon the progresses in bio-assays of clinical pharmacology, the USA Food and Drug Administration (FDA) made a policy change known as Hatch-Waxman Act in 1984, which officially determined the human pharmacokinetic bio-equivalence (BE) to replace traditional RCTs for developing generic medications.<sup>4</sup> As a result, the BE policy was also implemented for chemical generics by European Union in 2009.<sup>4</sup> Consistently in 2016, Chinese State Council initiated a campaign requiring the quality of generic drugs be re-evaluated through running clinical BE studies, compared to that of original reference products.<sup>5</sup>

In the field of innovative medicine, dramatic breakthroughs from life science have revolutionized our understanding in a number of aspects of disease biology, including therapeutic targets and diagnostic biomarkers,<sup>2,6</sup> thus inspiring some flexible modification of

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traditional RCTs in order to deliver novel medicine to the patients in need more efficiently.<sup>3</sup> Accordingly in late 2016, the 21st Century Cure Act was passed into law by US Congress, and instructed FDA to update the adaptive design guidance for investigational drugs and biological therapies.<sup>7</sup> To date, certain modes of these updated trial protocols have exceptionally contributed to timely translating contemporary scientific discoveries into innovative drugs that addresses unmet clinical needs.<sup>2,8</sup> In this light, the article herein highlights an array of outstanding developments in the perspective of drug trial design, being corroborated by notable successes in the clinical settings (Table 1).

## CLINICAL BIO-EQUIVALENCE

**Concept.** The idea of BE is allowing equivalent pharmacokinetic exposure to replace RCTs, particularly in case of comparing a generic medication to its reference product.

**Principle.** It has been well recognized that pharmacological effects of drugs are dependent on their targeting tissue concentration which is usually proportional to their distribution in circulation system, known as bio-availability. Of note, the latter can be affected by various pharmacokinetic-associated factors including active compound, formulation, manufacture, drug-drug interaction, among others.<sup>4,9</sup> In this sense, major pharmacokinetic parameters, such as area under curve and maximal concentration (C<sub>max</sub>), are utilized as the surrogate parameters to compare efficacy and safety of a generic agent with those of the reference drug in clinical BE studies.<sup>9</sup> Most drugs are thereby accepted to be therapeutically equivalent when their area under curve and C<sub>max</sub> fall in the range between of 80% and 125% regarding limits of 90% confidence interval.<sup>4</sup> While having been significantly contributing to development of most chemical generics, BE is recently

noted as an efficient approach that can not be completely replaced by in vitro methodology even in some high solubility and high permeability products.<sup>10</sup>

**Application.** BE study is frequently applied for comparing certain innovative agents in terms of formulation changes or fixed dose combinations; for example just being approved in 2018, Consensi consists of a combination of amlodipine and celecoxib to treat concomitant hypertension and osteoarthritis.<sup>11</sup> Realistically for evaluating a generic version of the polysaccharide drug heparin, the activities of anti-factors Xa and IIa instead of pharmacokinetic parameters are used to be the official standard for human BE trials.<sup>12</sup> In consistent with the policy of FDA, European Medicines Agency has recently accepted the BE investigation in healthy human subjects for generic development of low molecular weight heparin without requiring RCTs in thromboembolism prone patients anymore.<sup>13</sup> Besides, utility of BE study is being expanded into the field of evaluating biosimilar products such as antibodies and fusion proteins which represent much larger and more complex molecules.<sup>4</sup> Interestingly based upon a human BE investigation in healthy volunteers and noninferiority RCTs in the patients, the biosimilar version of etanercept, a medication of fusion protein neutralizing inflammatory cytokine tumor necrosis factor- $\alpha$ , has just be approved for managing rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.<sup>14</sup>

## PHASE 0 CLINICAL STUDY

**Concept.** Phase 0 trial defines the exploratory clinical studies with the drug exposure less than that in phase I trials, to facilitate translation in drug development.

**Principle.** Contemporary pharmaceutical innovation is facing a serious reality of declined successful rates from research and development, in contrast to much more new

**Table 1.** Representative examples of innovative clinical trial designs

Trial mode	Unique feature	Examples discussed	References
Bioequivalence	PK exposure replaces RCTs	Consensi biosimilar enoxaparin biosimilar etanercept	11 12 14
Phase 0 trial	Exploratory trial with microdosing	AZD1775 midazolam DDI	16 15
Seamless trial	Integrated trial without phase gaps	Keytruda indacaterol	18,21 22
Basket trial	One trial for numerous types of disease	larotrectinib Tafamadis	27 28
Therapeutic re-purpose	Shifting therapeutic indication during a trial	sildenafil crizotinib empagliflozin	31 2,32 33
Orphan drug	Various expedited trial designs	xuriden tecovirimat imatinib	37 38 6,40

Abbreviations: DDI, drug-drug interaction; PK, pharmacokinetics; RCT, randomized controlled clinical trial.

compounds/new targets for examination in clinical investigation. In this regard to reduce a wast of the resources, FDA issued a guideline of an alternative approach for first-in-human trials in 2006, which was termed exploratory investigational new drug application (or phase 0) allowing a flexible amount of data needed for investigational new drug application based upon the specific circumstances of each proposed human trial.<sup>15</sup> Tending to bridge the gap between preclinical studies and traditional clinical development, phase 0 investigation differs from phase I trial in fewer human subjects, short processing time and no tolerability test. As a result, phase 0 study can accelerate the “go-or-no go” decision making prior to a formal RCT, namely improving the efficiency of identifying drug-like candidates and terminating non-promising compounds.<sup>15,16</sup>

**Application.** The strengths of phase 0 study have been validated in various aspects of drug development including intratarget micro-dosing, clinical pharmacology, vulnerable populations, among others.<sup>15</sup> Interestingly, microdosing of insulin through limb artery injection was capable of achieving targeted control of local glucose level with minimal systemic exposure of the drug<sup>17</sup>; it offered insights into local application of medications, in particular for those with narrow therapeutic windows, to deliver clinical efficacy precisely while remarkably diminishing the systemic toxic effects.<sup>18</sup> Impressively, an unique role of phase 0 trial has been recently highlighted in the drug development against brain tumor. As a cell cycle-associated kinase inhibitor, AZD1775 was revealed to have a strong anti-glioblastoma efficacy and poor blood-brain barrier penetration in preclinical studies. It was through a phase 0 investigation demonstrating that the compound substantially crossed blood-brain barrier and induced the expected biomarker alterations clinically, which thus made a moving-forward decision for this project.<sup>16</sup> Besides, microdosing study appears particularly beneficial for vulnerable populations in which new drug trials are restricted, including children, liver and/or kidney function impaired, multi-pharmacy, among others.<sup>15</sup>

## SEAMLESS CLINICAL DEVELOPMENT

**Concept.** Seamless clinical trials integrate the 3 phase-processing of RCTs into a comprehensive clinical study without phase gaps, whereas a classical trial consists of sequential 3-phases with interval times in between for analysis to determine the next design.<sup>2,3</sup>

**Principle.** While reserving the core strength of traditional clinical trials in terms of defining efficacy and safety regarding tested compounds, seamless clinical study significantly improves time and cost efficiency to translate

the scientific breakthroughs into innovative medicine.<sup>2</sup> A seamless phase I/II design is to examine the toxicity and efficacy in 1 trial, during which a reasonable dosing set need to be screened out at the first stage, and then forwarded to evaluate the efficacy at the second stage.<sup>3,19</sup> In a similar sense, a seamless phase II/III trial is performed with the investigated drug at the exploratory stage to define the most efficacious dose based upon some surrogate end-points such as objective response rate (ORR), and this dose is then continued into the confirmatory stage for further testing without a timing gap, to obtain more definitive end-points such as overall survival.<sup>8,19</sup>

**Application.** Given the flexibility for modification upon interim analysis, seamless development allows to study accumulating data from the ongoing clinical trial for early assessment of toxicity, efficacy or futility, and thus to decide the terminating or continuing and/or expanding treatment arms accordingly for further investigation.<sup>19</sup> It was through a well-designed seamless (phase I-II) clinical trial that the programmed death 1-blocking antibody keytruda achieved accelerated approval (AA) by FDA.<sup>2,18</sup> In this scenario, a dosing-escalation study was carried out at the first stage of the trial, to evaluate safety, tolerability and possible efficacy (ORR) in a spectrum of patient cohorts with advanced cancer of various types.<sup>18,19</sup> Based upon the interim analysis, the cohorts of melanoma and non-small cell lung cancer (NSCLC) were determined to be expanded for the continuing clinical trial on treatment with keytruda at the selected dosages of 2 mg/kg or 10 mg/kg.<sup>20,21</sup> As a result, keytruda was demonstrated to confer a therapeutic benefit for the patients with melanoma (ORR: 38%~40%) and NSCLC (ORR: 19.4%); moreover, with the biomarker stratification of programmed death-L1<sup>+</sup> above 50%, an even better ORR (45.2%) was achieved in the subset of patients with NSCLC.<sup>21</sup> Additionally, beyond successful application for oncological drug development, seamless clinical study has substantially contributed to therapeutic innovation in other medical fields.<sup>3</sup> Of note, the efficiency of clinical developing inhaled indacaterol, a long-acting  $\beta_2$ -agonist for treatment of chronic obstructive pulmonary disease, was clearly improved through a seamless (phase II-III) clinical trial.<sup>3,22</sup>

## BASKET CLINICAL TRIAL

**Concept.** In a basket trial, the testing compound is simultaneously examined across numerous disease baskets, to reveal the therapeutically sensitive subset of patients within each disease type.

**Principle.** Historically human disease is categorized and managed according to anatomic location of body organs and histological types of pathology, which forms a solid

basis for therapeutic indications designed in conventional clinical drug development.<sup>23</sup> However, since the rise of targeted medicine in recent 2 decades, the landscape of pharmaceutical innovation has been transformed to modulate an aberrant biological pathway that can contribute to pathogenesis across a number of diseases,<sup>24</sup> such as a gene mutation occurred in various neoplastic disorders.<sup>25</sup> Intriguingly, a mutational target is typically present only in a portion of the patients with each tumor type due to interpersonal heterogeneity, thus inspiring emergence of basket trials in the clinic.<sup>2,23</sup> In this light, basket trial can be designed to examine an innovative medication in a wide spectrum of different cancer types, in order to determine not only whether the drug is efficacious but also what tumor types and more precisely which patient subsets are sensitive to this therapy.<sup>23,25</sup> The first stage of a basket trial is to select the therapeutically sensitive disease types and patient sub-populations, with a biomarker-based companion diagnosis if possible.<sup>19,26</sup> Following interim analysis, the futile tumor type baskets are terminated, and the efficacious subjects are enriched from the responsive baskets, to be thus forwarded to further clinical investigation at the second stage.<sup>23,26</sup>

**Application.** As a selective tropomyosin receptor kinases (TRK) inhibitor, larotrectinib represents the newly approved medicine targeting a wide spectrum of tumor types, reflecting a dramatic success of basket clinical study.<sup>25,27</sup> Aberrant TRK activation drives oncogenic pathogenesis, and is expressed in more than 20 distinct tumor types. Nevertheless, except a few types of rare neoplasms such as congenital fibrosarcomas, TRK alterations occur in very low frequencies in common cancers of various tissue/cell lineage origins, for instance below 5% in lung adenocarcinoma.<sup>26</sup> Based upon a basket trial design to investigate the clinical efficacy of larotrectinib, the subjects were selectively enrolled from patients with the aberrant TRK activity in tumors across 16 histological types. Impressively, larotrectinib was demonstrated to be well tolerated, conferring an ORR of 80% and a median progression-free survival of 9.9 months.<sup>25,26</sup> As such, this novel targeted agent stands out to address the unmet clinical need of combating the rare neoplasms and numerous common tumor types with the rare genetic mutations.<sup>26,27</sup> Besides the validation in field of anticancer drug development, basket clinical has been proposed to go beyond oncology into cardiology, such as heart failure with preserved ejection fraction (HFpEF) across diverse etiologies, pathobiologies, and clinical presentations.<sup>28</sup>

#### THERAPEUTIC RE-PURPOSE DURING CLINICAL TRIAL

**Concept.** Therapeutic re-purpose aims to identify the best benefit(s) of a testing drug against disease through

dynamic change of the medical indication(s) during clinical trials based upon accumulating efficacious data or/and cutting-edge scientific discoveries.<sup>7</sup>

**Principle.** Depending on bio-medical contexts, such dynamic updating of clinical applications may be pre-planned or inspired by certain serendipitous observations, through shifting from a therapeutic hypothesis to an alternative one or multiple ones.<sup>2,29</sup> In this sense, a study design allows to examine beyond the intend-to-treat disease, thus being re-purposed to an alternative indication according to the initial assignment upon lack of efficacy or safety issues<sup>7</sup>; otherwise, a clinical trial can also be optimized to cover more therapeutic directions with the emerged evidence of certain additional efficacy.<sup>24,30</sup> In the era of precision medicine, there has been a consensus that therapeutic outcomes can vary significantly among subgroups of patients with differential genetic profiles.<sup>2,27</sup> Accordingly taking the advantage of interim analysis based on novel biomarker approach for detecting the pathogenesis-specific molecular alteration(s), an adaptive clinical study can select the drug-sensitive sub-population from patients with initially targeted disease or an alternative indication, to continue the investigation for an optimized therapeutic efficacy.<sup>7</sup>

**Application.** As a selective 5-phosphodiesterase inhibitor, sildenafil was designed to manage angina pectoris in the initial clinical trial. Disappointingly this compound appeared nonefficacious in relieving anginal pain, with a side-effect of inducing penile erection.<sup>31</sup> Inspired by this serendipity, the clinical development was successfully re-directed to come up with a major innovative product of anti-erectile dysfunction.<sup>29,31</sup> In the field of oncology, crizotinib was initially identified as a potent inhibitor of mesenchymal–epithelial transition factor, thus tending to treat the relevant neoplasms such as NSCLC and gastrointestinal tumors.<sup>2</sup> Whereas this compound was then revealed to suppress anaplastic lymphoma kinase (ALK) as well, and impressively to exert a clear efficacy of tumor shrinkage in the NSCLC with ALK rearrangement during a phase I clinical study. In this regard, the therapeutic indication of crizotinib was re-focused and successfully developed through following-up clinical trials, to be a precisely targeted medication for managing a subset of lung cancer patients with ALK aberrations.<sup>2,32</sup> Interestingly in recent years, besides serving as an exceptional type of medicine for controlling type 2 diabetes, the clinical trials of sodium glucose cotransporter 2 inhibitors are being expanded or re-positioned to manage heart failure and protect renal function through blood glucose lowering-dependent or/and -independent mechanisms.<sup>29,33</sup>



## ORPHAN DRUG AND CLINICAL TRIAL

**Concept.** Orphan drugs are developed to treat a particular spectrum of medical conditions known as rare disease, usually through the clinical trials of various expedited designs with possibilities of further simplification.

**Principle.** Of note, definition of rare disease varies among different countries depending on epidemic incidence of each illness geographically.<sup>34,35</sup> To address this largely unmet clinical need and meanwhile to deal with the challenging issue of limited market size for profits, FDA announced an incentive policy known as the Orphan Drug Act in 1983, offering research & development funding, market exclusivity, among other attractive benefits.<sup>35</sup> Since then there were similar policies coming forth from other countries, encouraging an increased interest in this regard for pharmaceuticals; orphan drugs have been representing more than 40% of innovative medications marketed through last 3 decades.<sup>34</sup> Interestingly in recent years, certain orphan drugs are revealed to be overlapped with blockbuster products, which appear more notable in the field of oncology.<sup>18,21</sup> In this scenario, a novel medicine can be initially approved for a rare disease, and subsequently go beyond to treat additional types of disease; vice versa a conventional drug may occasionally obtain orphan status upon expanding its therapeutic indications toward a rare medical condition.<sup>21,34</sup>

**Application.** Clinical development of orphan drugs often involves expedited trial designs described above, and may even be further simplified or alternatively designed under particular circumstances.<sup>35,36</sup> For instance, the approval of orphan drug xuriden was based upon a minimal seamless trial for 6 weeks with only 4 patients, to treat hereditary orotic aciduria representing a rare disease of only 20 cases worldwide.<sup>37</sup> In addition, a viral inhibitor tecovirimat has recently been authorized to treat smallpox upon the waive of clinical efficacy study due to lack of patients with the naturally occurred disease. Setting the first record in regulatory history, this innovative medication was exceptionally approved based on positive results from the preclinical efficacy studies in animal models of rabbits and monkeys, along with a phase I trial of clinical pharmacology and safety in healthy human subjects.<sup>38</sup>

Impressively, certain orphan drug-based clinical trials can also come up with a broad spectrum of efficacy covering multiple indications. As a hallmark success of targeted medicine with orphan status, to combat Philadelphia chromosome-positive chronic myelogenous leukemia imatinib was launched onto the market through the AA following a phase II trial consisting of 3 open-label, single-arm clinical studies.<sup>6,39</sup> Moreover, imatinib was subsequently evaluated in a basket clinical

trial and demonstrated to be efficacious for an array of extra-therapeutic indications beyond chronic myelogenous leukemia, dramatically transforming this orphan drug toward being a blockbuster medication.<sup>40</sup> Besides, an interesting basket clinical study has recently been designed to investigate a target-specific monoclonal antibody for controlling an array of complement-mediated rare disorders, including bullous pemphigoid, antibody-mediated rejection of organ transplants and and warm autoimmune hemolytic anemia.<sup>41</sup>

## PERSPECTIVE

Clinical trial plays an indispensable role in evaluating efficacy and safety of therapeutic agents prior to marketing for human use, and has been constantly evolving along with the dynamic interactions between cutting-edge scientific discoveries and regulatory policy updating.<sup>2,3</sup> In this light, a number of agile clinical developing modes were designed through past decades, and impressively some of them have been further corroborated upon the y achievements evidenced by successfully delivering innovative medicine to the patients in a more efficient manner.<sup>7</sup> While human BE study is increasingly contributing to evaluation of emerging formulation and bio-similar agents besides chemical generics,<sup>4</sup> several adaptive trial designs have been capable of translating the scientific breakthroughs into novel therapeutic benefits with shorter processing time and lower financial costs, to address the unmet clinical needs.<sup>3,19</sup> Moreover with the assistance of bio-marker-based companion diagnosis, certain innovative trial designs have been streamlined to precisely confer selective therapeutic efficacy to the responding subgroups of patients with an array of serious diseases in particular certain types of cancer.<sup>6,27</sup> It is conceivable that these innovative trial modes would be inspiring for coming waves of clinical drug development against the emerging severe illness without specific treatment such as COVID-19 infection.<sup>42,43</sup>

Of note, to preserve the strength of clear defining efficacy and safety of tested drugs, the innovative designs of clinical study are substantially overlapped with classic trial protocols of 3 phases which still serve as the mainstream approach of clinical investigation.<sup>3,7</sup> Realistically, the medications through expedited processing appeared having a higher rate of postapproval black-box warnings than that of regularly approved drugs in terms of safety issues.<sup>44</sup> It has accordingly been proposed that single-armed phased II studies to be accepted only for AA applications regarding refractory diseases. Otherwise, interim analysis of ongoing phase III trials may be able to support AA processes, with the

follow-up studies required to provide further evidence for the drug's effects on human bodies.<sup>45</sup> Whereas precision medicine-inspired trials represent an unique highlight in contemporary clinical studies to optimize the therapeutic efficacy for preferable subsets of patients with certain diseases upon enrichment strategies,<sup>3,27</sup> the validated biomarkers are limited and even much less than established drug-target molecules.<sup>2,46</sup> Moreover, there still is a lack of the biomarkers to predict drug-triggered adverse events such as heparin-induced thrombocytopenia or immune checkpoint inhibitor-resulted hyper-progressive disease.<sup>47,48</sup> Hence, it takes a dialectic perspective to appreciate the high efficiency of these innovated designs, with mindful efforts on circumventing their imperfectness.

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