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Pharmacovigilance 2020: Innovative Clinical Trial a Gold Standard for Optimization of Clinical Drug Development- Ibrahim Aminu Shehu- Sharda University

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ABSTRACT:
Traditionally, a randomized clinical trial (RCT) is known to be the mainstream for novel drug development and a pipeline for therapeutic and safety evaluation of any drug candidate before entering into the market. Unfortunately, it takes tedious and complex protocols that consume huge amounts of resources, labor, and time. Therefore, these pose several limitations in conducting the trial, and this includes; limiting the CT study period, recruiting a small number of participants, and lack of funding by the sponsors, which in turn expedites the safety and efficacy failure, as well as the chances of several adverse drug events following the market feedback. Thanks to the recent innovations in clinical trial space that allows the flexible modifications of RCT, which consist of the evaluation of human pharmacokinetic bioequivalence, the inclusion of phase 0 stage, and adoption of "master protocol" in clinical trial design, among others. The previously mentioned strategies bring about the study flexibility and upper potential solutions to the inherent limitations of RCTs. This research survey in-depth literature on the specific research keywords in the recognized global scientific databases like PubMed, Elsevier, Science Direct, Google Scholar, et al. More so, we focus on highlighting the recent strategies adopt in designing the innovative clinical trials along with their associated benefit and perspectives.
Keywords: Randomized clinical trials RCT, Innovative clinical trial, novel drug development, master protocol, Phase 0

INTRODUCTION:
Since the 1940s, [1] the traditionally authorized means of establishing the safety and potency of any drug before human consumption is through Randomized clinical trials (RCT). Moreover, RCT is still an official protocol used for licensing any drug to market. Although, the implementation involves a complex process from phase I to II and thus, associated with several challenges including high cost of implementation, long and tedious duration, lack sampling, and subgrouping. [2] These attributes to the clinical trial failure of some drugs in the market. In recent years many molecules are getting their way to clinical trial than before, but the extent of the failure of these molecules remains a huge challenge in the pharmaceutical research field.[3] Perhaps, as more molecules are recruit into CT stage the rate of FDA approval to market generic drugs was sharply declined by 14% since 1985. [4] In the sense that only less than 10% of IND filed molecules got FDA approval for marketing. Furthermore, the 75% cost associated with CT of generic drugs was found to have linked with the occurrence of a high failure rate. [5]

Consequently, USFDA, Pharma/biotech industries, and Academic research teams joined hands on deck to find out the possible reasons and suggest the solutions to these challenges through providing some means of fine-tuning the conventional means of drug regulations and guidelines. [6] The benefit of re-valuating the mainstream of CT would significantly counteract the current declination of new drug development, reduce 10 - 15year duration of course s of CTs and subsidies the billions of US dollars spent on the process of developing the generic drug. [7,8] Therefore, this study focus on highlighting the novel innovations in Clinical trial settings along with their associated benefit, perspectives, and challenges.

THE CLINICAL BIO-EQUIVALENCE STUDY:
The Clinical Bio-Equivalence study is among the most significant aspect in establishing the drug pharmacokinetics and dynamic profile, therefore, pharmacokinetic parameters like Concentration maximum (Cmax) and Area under the curve (AUC), reflect true safety and efficacy of the generic drug in comparison to clinically bioequivalence. The acceptable bio-equivalence range lies between 80 - 120 % at 90% confidence level. [9] Perhaps, the in vivo studying is not enough to surrogate bioequivalence study completely. [10,11] In recent scenarios, a fixed-dose combination of amlodipine and celecoxib was approved in by FDA 2018, indicated to treat the comorbid condition of hypertension and osteoarthritis.[12] Likewise, European Medicinal Agency EMA approves human trials of low molecular weight heparin on the bases of Bio-equivalent study, not RCT. [13]

PHASE 0 TRIAL
Because of the inherent challenges associated with RCT of oncology drugs, and their subsequent failure rate that accounts for over 90% [14] Food and Drug Administration FDA established a joined Task Force that comprises the group of

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experts from, Pharmaceutical industries, National Cancer Institute (NCI), and Academia. The task force enacted to evaluate the methodology for the development of innovative cancer therapies (MDICT). [15] Following the series of interactions, they have issued a Critical Path Report in March 2004 that proposes the inclusion of phase 0 study in CT. [3,16] Consequently, The exploratory IND accepted their appliance by approving its immediate implementation. However, the concept of Phase 0 involved testing a low dose of a drug candidate to a small number of patients (less than 15) for a short study period with low toxicity risk. [17] The PK /PD and outcome of these patients will signify the inclusion or otherwise of the most promising drug or its analog into phase I CT stage. Therefore, the burden and the rate of CT failure could significantly be subsided. [17]

Benefits:

1. Establishment of features of a molecule agent with few numbers of patients in a short of time.
2. Enhances the success rate of molecules in development Guide go/no go decisions for subsequent clinical development
3. Ease the decision making in which candidate or analog to enter phase I CT
4. Provide better approximation of active and safe starting dose for phase I trials
5. Pathway for selection of best candidates among its analogs.
6. Significant reduction in CT cost, duration, and risk of toxicity

Limitations

1. Dose extrapolations could result in problems due to nonlinear PK.
2. Misappropriation in result declaration may lead to the withdrawal of promising candidates
3. Not all drugs are a suitable candidate for phase 0 trials trial.

MASTER PROTOCOL

Likewise, the master protocol is another tending aspect of innovative CT; it is designed to target multiple diseases with a single drug candidate or a particular disease with multiple drugs in a single trial. [18] This means of subgrouping population emerges as an incredible procedure that came on board in 2006 [19] as a result of huge success gained by "Novartis" following pre-phase II approval of Imatinib Mesylate by the FDA. [20] Imatinib Mesylate is a product indicated to have target 5 different cancer types. However, in 2019 both FDA and EMA have issued a manual of recommendations to aid the implementation of such CT innovative designed [20,21]

Basket: In this protocol, single drug is tested on multiple disease by subgrouping the patients and subjecting them to parallel sub studies.

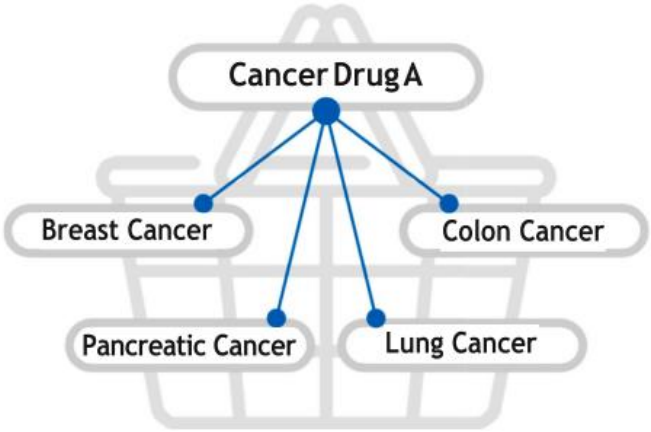

Fig. 1. Example of basket trial design.

Umbrella: This involved the recruitment of many molecules for targeting common disease. Therefore, the patents are sub grouped into parallel arms and treated with different drugs and combinations.

Platform: It also employ the multiple treatment of common disease with several drugs, single or combine regiment. The exit and enter decision is done on the bases of outcome of response - adaptive ran domination (RAR) rules assessed from algorism model.

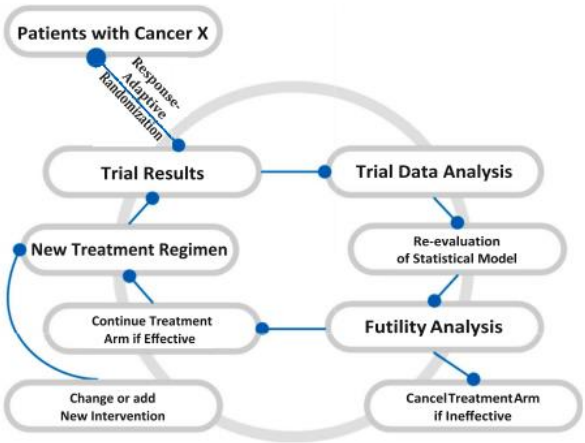

Fig. 3. Example of PlatformTrial design.

CONCLUSION:

Innovative clinical trials can serve as a gold standard model to optimize clinical trial processes, by shortening the study period, minimizing the cost and failure of CT, while maximizing the safety, economic and therapeutic benefit. Therefore, shortly, there would a chance of innovating some drug products bearing multiple indications within a short period with less labor and funding. Equally, the therapeutic choice of targeting many diseases will also be maximized.

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