A Review of Drug Discovery, Development and Clinical Research

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***Abstract* — Physical, social and mental state of well being is known as health. Reportedly, there are 4000 diseases in the world, out of which we are able to treat 6% of them using drug. Discovery of drugs therefore remains a mainstay of research now days. Out of thousands or millions of molecules, only one (or two) can make their way to successfully become approved drug. Therefore, current review is focused on drug discovery aspects which includes search from therapeutic need to molecule and drug development which includes research from molecule to product registration in market.**

***Keyword* — Clinical research, Clinical Trials, Audits, Clinical Data Management.**

I. Introduction: Need of drug discovery

Health is most important concern for human being across the globe. World health organization (WHO) defines it as state of physical social and mental wellness [1]. However, diseases exist since evolution of man from apes. Different types of diseases cause death and reduce life expectancy of human population. According to Francis Collins, Director of National Institute of Health USA (NIH), we have knowledge of molecular causes of only 4000 diseases and out of them we have been successful to treat only 6% of them using drugs [2]. WHO has released projections of mortality and causes of death for year 2015 and 2030 [3]. Out of them; ischemic heart disease, stroke, lower respiratory tract infection, chronic obstructive pulmonary disease, diarrheal diseases, HIV, respiratory cancers, diabetes, road injury, and hypertension rank in order 1 to 10 in the table [3]. Therefore, it is essential to discover drugs for these top causes as well as rest of gap that is remaining to fill in current therapeutics. Apart from this, increasing percentage of orphan diseases is also important concern to focus on drug discovery. Diseases such as Progeria, Beta thalassemia, Parkinson's and Alzeimer's disease are occurring in very less number of population across the world. Therefore, drug makers cannot make much profit out of this discovery. Such diseases are called orphan diseases and drugs to treat them are called as orphan drugs. Cost of drug development in these cases could not be recovered from sales of drug [4]. Third reason for need of new drug discovery could be patent fight amongst innovator pharmaceutical companies. One newly discovered molecule ideally gets 20 years life time for patent exclusivity, out of that minimum 5 years exclusivity is gained by company to market it into that country [5]. Fourth need of new drugs discovery is unmet therapeutic need. These are diseases wherein we are unable to find solutions till this date. These include schizophrenia [6], uterine myomas [7], multiple sclerosis [8], and eosinophilic esophagitis, etc [9].

II. Cost of drug discovery and development

Drug discovery and development is costly affair. Out of thousands or millions of molecules, only one (or two) can make their way to successfully become approved drug. Drug discovery involves different steps right from target identification to clinical development. Very few molecules make their way to clinical development and ultimately one or two get successful way till approval from regulatory authorities [10]. Different studies indicate different figures about cost of drug discovery. Dickson and Jagnon et al. [11] suggest that it is more than US $800 million in year 2004. Tufts Center for study of drug development in November 2014 suggested that cost is now US $2.6 billion (i.e. US $ 2,558 million) which includes US$1,395 million as out of pocket expenses and US $ 1,163 million as time cost. [12] However, Matthew Herper from Forbes suggested that this figure is US $ 4.2 billion after studying costs of new drugs from 100 companies across the globe [13]. From these figures it is evident that drug discovery is costing very high. This could be due to long process and patenting regulations. More interestingly, in list of top 10 R&D spenders amongst all world, four drug companies namely, Roche, Novartis, Johnson and Johnson and Merck have achieved the position [14].

III. Drug discovery and development: Steps in detail

Discovery and development of new drugs which could be probable answer for clinical benefit is essential process. Development of new drug provides answers to unanswered clinical questions. Classically speaking, drug discovery and development is recognized into following steps (Figure 1):

Target identification; target validation; lead identification; lead optimization; preclinical studies; clinical research with phase 0, I, IIa, IIb and III; and post marketing studies [10]

Investigational new drug application (IND) is submitted after pre-clinical or non-cliinical studies so as to get permission to conduct clinical trial. Product registration or marketing authorization submission is submitted regulatory authority at the end of Phase III clinical trial.

Thus from above steps, drug discovery could be broadly classified into three steps [10]:

- Drug discovery which includes search from therapeutic need to molecule
- Drug development which includes research from molecule to product registration in market
- Commercialization which includes steps from product to therapeutic use to sales of drug.

Before the start of drug discovery project, it is necessary to consider strategic issues, scientific and technical issues and operational issues for the pharmaceutical company.

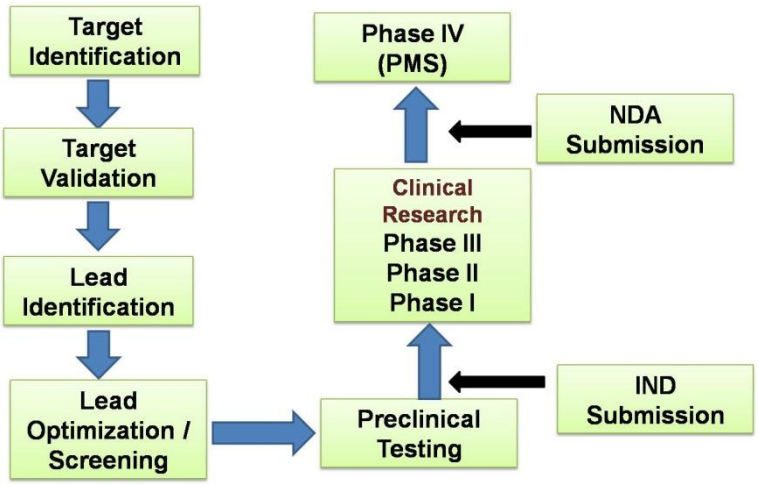

Figure 1: Drug discovery and development process with regulatory milestones for approval (Figure redrawn from reference 10)

Target identification

Starting of drug discovery research is usually done with identification of target which is in fact a molecular protein or receptor or gene which has close relationship with disease causation or progression. Ideal target should have characteristics such as it is 'druggable', safe, effective and suitable to meet clinical needs [15]. Data mining of existing available biomedical data16 and phenotypic screening are methods used to identify appropriate targets. Targets can be further classified into three types: speculative research targets, innovative improvement targets and me too targets. Speculative targets can be exemplified by HMG-CoA reductase inhibitors and ACE inhibitor drugs [17]. Innovative improvement targets give the drugs that show improvement in characteristics of existing drugs [18]. Following table 1 shows this fact.

Category	Propranolol	Atenolol
Beta selective	No	Yes
Dose/ Day	3 times a day	1 times per day
Dose	High	Low
Safety	Less	Better

Table 1: Example of drug obtained from innovative improvement targets

Third type of targets are me too targets. Me too drugs are those molecules that are having similar chemistry as that of prototype drug with same mechanism of action. They are not showing significant improvement in action when compared to prototype [19], [20]. Examples of drugs include bisoprolol, betaxolol that have actions similar to prototype atenolol.

Target validation

Target validation involves identification and assessment of molecular target (e.g. receptor) to determine whether it meets requirements to produce therapeutic effect. During this study, computational software is used to determine association of drug targets with specific disease under consideration. This step requires time period of approximately 6 months to 1 year [21-22].

Both target identification and validation were graphically represented by Hughes et al. [15] in Figure 2.

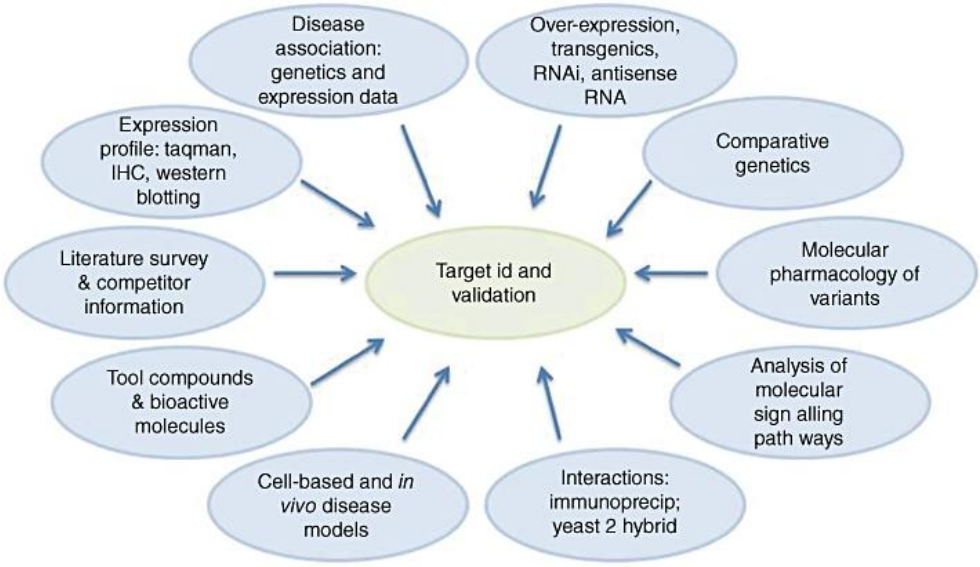

Figure 2: Target identification and validation: Processes view
(Adopted from Hughes et al. [15] Used without permission. For academic purposes only)

Lead identification

After target validation process, it's time for lead identification by identification of 'hit' which involves different screening assays. Lead is defined as any chemical or biological compound that binds and interacts with receptor (i.e. validated target) to show expected biological activity to have desired therapeutic action. This molecule is further attached with different functional group for refinement of structure to reduce adverse effect and improve its therapeutic benefit. For a compound to become successful drug, it would have obeyed Lipinski's rule of five or Pfizer rule or rule of five (RO5). This rule has following important points:

1. Molecular weight of newly discovered compound or potential candidate should be less than 500.
2. It should have less than five hydrogen bond donating functions
3. It should have less than 10 hydrogen bond accepting functions
4. It should have log P values of -1 to +5 approximately.

Lipinski's rule of five or Pfizer rule or rule of five (RO5) is widely used rule of drug discovery that helps in identification of ideal properties of drug or drug likeliness. Christopher Lipinski evaluated more than 2000 drugs and finalized these criteria [23]. To overcome loopholes of Lipinski rule, many metrics were tried such as ligand efficiency24, lipophilic ligand efficiency [25], etc. were tried by researchers. Prof. William L Jogrensen designed similar rule like RO5 rule which evaluates acceptability of analogues based on RO5 rule [26].

Sources of leads

In current drug discovery research, majority of leads are obtained from chemical libraries. However, in old days, nature was one of the best sources to find the drugs. Following discussion provides a short overview of hits, leads and candidate drugs obtained from different sources.

a) Higher plants and animal products [27]:

From ancient times, it was proved that plant and animal products have some medicinal properties. Complementary and Alternative Systems (CAM) of medicine like Ayurvedic, Unani and Homeopathic system have used the many plant and animal products as sources of drugs. With the use of fundamental principles of CAM or nature resources, drugs were extracted from natural sources or they are modified chemically to obtain desired characteristics. Drugs from different categories such as taxol (anticancer), anti-infective, aspirin (analgesic), cocaine (anesthetic) etc are derived from plant sources. Development into genetic engineering helps to produce different hormones for eg. Insulin for diabetes mellitus, hormones for replacement therapy are derived from animal sources.

b) Arthropod and insect products [28]

Leads can be obtained from arthropods and insects. Batracotoxin is currently studied for its cardiovascular effect. It is an alkaloid isolated from the skin of certain colorful tropical tree frogs. Further comprehensive studies have shown that these alkaloid are not directly produced from the tree frogs but are accumulated from digestion of arthropods that make up much of their diet.

c) Fermentation products

Many micro-organisms such as bacteria, fungi survive on dead plants and animals. They degrade these products and produced different kinds of antibiotics. Penicillin is one of the most well known examples of the fermentation product from yeasts [29]. Some of cytotoxic drugs are also produced to treat tumors [30].

d) Marine products

Seven seas are the rich source of compounds to find drugs for different disorders. Many cytotoxic drugs such as eleutherobin, discodermolide are presently tested for the anti-tumor potential [31]. The more intensive studies should be done to discover more products.

e) Repositioning old drugs

To find a single promising drug, thousands of compounds were screened. These compounds were failed to give activity or the safety criteria for the desired category. These compounds can be tested for different therapeutic categories and can be used for different disorders. This is called as drug repositioning [32]. Drug repositioning offers advantages such as reduction in drug discovery costs, reduction in time of development and approval, etc [33]. Following table enlists different drug molecules with their old use and repositioned uses.

Drug	**Existing use in disease**	**Repositioned use in disease**
Aspirin	Non steroidal anti-inflammatory drug (NSAID)	Antiplatelet [34]
Bromocriptine	Parkinson's disease	Diabetes mellitus [35]
Gabapentin	Epilepsy	Neuropathic pain [36]
Methotrexate	Cancer	Psoriasis, rheumatoid arthritis [37]
Zidovudine	Cancer	AIDS [32]
Atomoxetine	Antidepressant	Attention deficit hyperactivity disorder [38], [39]

Table 2: Repositioning of existing drugs for new indications (diseases)

f) Combinatorial libraries [40], [41]

Drug is a complex chemical structure which binds with receptor or enzyme in body. Before, combinatorial technique was introduced in drug discovery, scientist used to design and synthesize the drugs and test them for biological activity. This utilizes plenty of time and money. After development of high-throughput screening methods and new tests, time required for the screening of compounds is decreased significantly. Combinatorial chemistry is a method of choice to produce large number of drug like compounds to develop new entities. Protein molecules are also synthesized by Merrifield peptide synthesis.

In combinatorial chemistry, substances are added simultaneously in different systems and in different order to produce different combinations of the compounds. These compounds are then screened for the biological activity to find the hits. Simultaneous production of compounds lower the time and cost of the drug design program [41].

Different methodologies used to construct the large molecules are single resin/single peptide (Merrifeld style), Combinatorial mode: mix and split style, Combinatorial mode: label, mix and split style, Radiofrequency detection, Deconvolution, Iterative deconvolution, Positional deconvolution, Omission and tester libraries, The Pasteur-Like Method , and Spatially Addressed Libraries which includes Photolithographic Method, Pin Method, and Tea Bag Method [41]. Following figure illustrates Merrified peptide synthesis method which is widely used for synthesis of drugs [42].

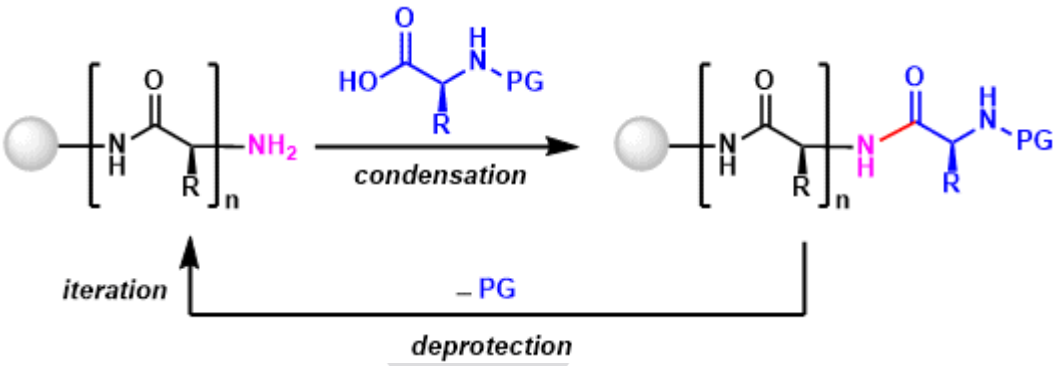

Figure 2: Merrifield style peptide synthesis [42]

Lead optimization techniques

Different lead optimization techniques are used in drug design of small molecular drugs. Some of them were described here in brief.

Determination of intermolecular reactions

Thermodynamic interactions, physical, free energy and individual group contributions help in determining intermolecular reactions to become best suitable drug. Estimation or evaluation of physicochemical properties is of paramount importance in drug discovery. These help to evaluate fitting or association of drug's chemical groups to receptor i.e. target. Thermodynamic interactions; physical characteristics such as electrostatic and steric interactions; entropic contributions; free energy perturbation and individual group contributions are helpful in estimation of intermolecular reactions so as to determine ligand receptor interactions. Garbett and Chaires [43] reviewed about use of thermodynamics in drug design process. Free energy calculations are

helpful in estimating interaction of drug with receptor. Shirts MR has reviewed about best practices in free energy calculations [44]. Homer et. al has detailed use of free energy in lead optimization [45]. Use of individual group contributions in drug design was described by Krogsgaard-Larsen [46]. Changes in free energy (delta G) give prediction of binding affinity or ability of new drugs. However, determinations in change of energy should be accurate, as small change in estimation could lead to large change in amount of dissociation constant of ligand (Kd). Perturbation techniques that are used in binding studies of ligands suffer from disadvantages like high cost of computation and only very closely related ligands could be studied. Hydrogen bonds are having role in interactions of long range, dipolar behavior and alignment of components of molecule to biological system.

Conformational analysis

Conformational analysis identifies different spatial arrangements of one molecule and such arrangements are differing in energies. Molecular dynamics, molecular mechanics, quantum chemical calculations, and analysis of experimental data of structures are the methods to determine conformations. Different conformational structures and their energies provide idea of best fit to receptor and thus help in detection of bioactive structure of drug. Calculations of conformational analysis (e.g. torsional driving) are time consuming and hence very rarely used in cases where more than two rotatable double bonds are involved [46]. Molecular dynamics, molecular mechanics, quantum chemical calculations, and analysis of experimental data of structures are the methods to determine conformations. Recently in 2015, Alesio Atozari has used conformational analysis for peptides and proteins for drug design using molecular simulations [47]. Since 20 years this method has been tried for drug design process [48].

Molecular superimposition techniques

These techniques are used to evaluate fitting of ligand in low energy confirmation. These are also used to investigate fitting of low affinity inactive ligands with model. These techniques are useful to confirm or discard the 3D pharmacophore model. Traditionally least square design is used to estimate molecular superimposition. Tanrikulu has reviewed pseudo-receptor based models in drug design [49]. Hoymer Alexander has done research on molecular superimposition of small molecules [50].

Pharmacophore modeling

An atom or group of atoms which are best fit to the receptor and have respective properties related to activity of compounds is called as pharmacophore. Pharmacophore has features in common for different compounds of the same chemical class. Pharmacophore modeling has been tried using ligand based, structure based, model based and virtual screening based methods. Using these approaches, many drugs were discovered. Concept of Pharmacophore has been coined by Paul Ehrlich. 3D pharmacophore models were tried successfully to discover new drug candidates46. Three dimentional pharmacophore modeling technique describes interaction of newly discovered molecule (ligand) with receptor. Rightly described pharmacophore along with properly positioned functional group attachments are helpful to discover small molecule chemical drugs. 3D pharmacophore modeling can also be used for identification of similarities between binding situations or two different binding molecules51. Pharmacophore modeling has been tried using ligand based, structure based, model based and virtual screening based methods. Using these approaches, many drugs were discovered [52]. Khdekar SA et al. have detailed about different tools such as CATALYST, GASP and DISCO that are used for pharmacophore modeling [53].

IV. ORGANIZATIONAL SCHEME IN DRUG DISCOVERY

Drug discovery and development is long process that takes around 12-15 years for successful launch of one single small molecular drug into market. Different departments have a role in this process. Following figure 3, shows role departments in drug discovery and development process.

Drug Discovery	Drug Development
Medicinal chemistry	Process Chemistry
Computational / Pre clinical biology	Pharmaceutics (Pre formulation and formulation)
Safety Pharmacology	Drug metabolism and safety assessment
Patent Department	Patent department
	Clinical Research
	Regulatory Department
	Marketing Department
Project management	**Project management**

Figure 3: Organizational scheme in drug discovery and development process (Adopted from presentation. © Amrit Karmarkar, 2013)

Before beginning of any project, pharmaceutical firms need to address strategies issues, scientific and technical issues and operational issues [10]. Use of collaborative environment between different departments will ease the process and also will make go/ no go decisions easier. Apart from intra-company organization, now day's different companies are joining hands for shared R&Ds. Open innovation model by Eli Lilly tries inventing new small molecular drugs through open innovation model by exchange of ideas between investigators, academic institutions and company. This will facilitate researcher with access to highly relevant screening assays and then further facility to collaborate with company for new drug discovery and development [54]. Shared R&D collaboration models include GSK-Imperial college, Astra-Imperial college, Merck-VGTI-FL, etc [55]. This shared innovation will reduce cost of early and late discovery.

V. PRECLINICAL RESEARCH

Next step after lead optimization or screening is preclinical research. It involves study of investigational drug on animals. Preclinical studies are conducted in two routes; one intravenous route and other intended route of administration of that dosage form. These studies are useful to estimate toxic effect of compound. Primarily, these studies involve short term and long term clinical studies. According to Schedule Y, preclinical studies are classified as systemic toxicity studies, male and female fertility studies, local toxicity studies, allergenicity / hypersensitivity studies, genotoxicity, and carcinogenicity studies [56]. Duration of non clinical program is very critical aspect and it needs to be discussed with regulatory authorities for clarification [10]. As general rule, duration of pre clinical trial corresponds to duration of clinical program. Duration of repeated dose toxicity studies that is necessary to support clinical trials is shown in table 3 as per ICH M3 (R2) guideline [57]. After obtaining data on safety in animals, investigational new drug application is submitted to regulatory authorities for permission to conduct clinical trial program.

Maximum Duration of Clinical Trial	**Recommended Minimum Duration of Repeated-Dose Toxicity Studies to Support Clinical Trials**	
	Rodents	**Non-rodents**
Up to 2 weeks	2 weeks	2 weeks
Between 2 weeks and 6 months	Same as clinical trial	Same as clinical trial
> 6 months	6 months	9 months

Table 3: Duration of repeated dose toxicity studies that is necessary to support clinical trials [57]

VI. CLINICAL TRIALS: PROCESS DETAILS

Clinical trials are way to achieve marketing authorization for new drug. They are of different phases such as Phase 0, I, IIa, IIb, III, IIIb and IV. Following is the general process for conduct of any phase of clinical trial. Following figures give outline of clinical trial operations process (Figure 4 to 8).

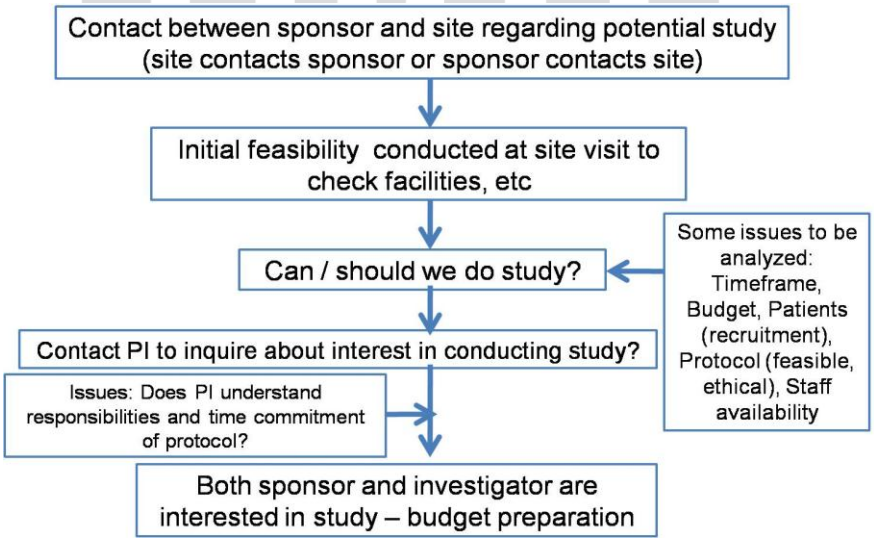

Figure 4: Ideal clinical trial operations process (Part 1 of flow chart) (Adopted from Gupta SK [58])

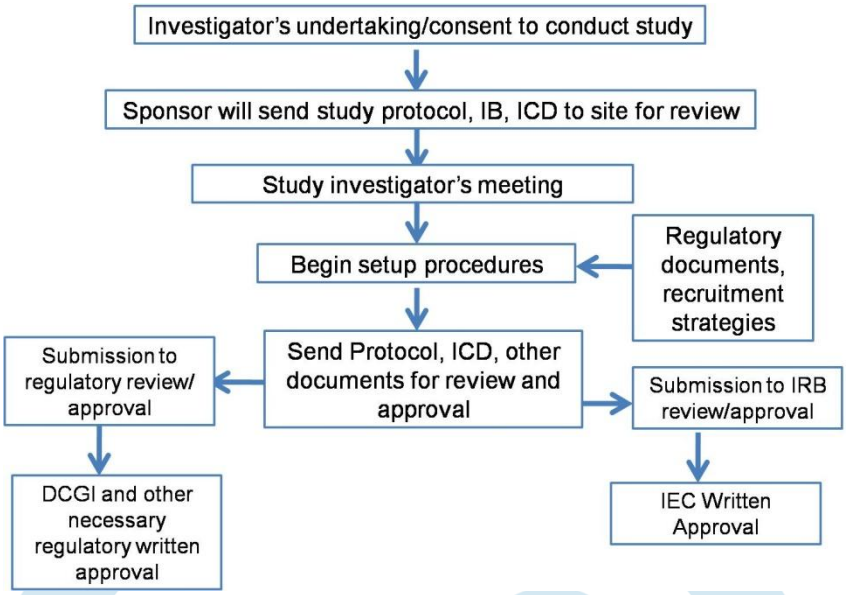

Figure 5: Ideal clinical trial operations process (Part 2 of flow chart) (Adopted from Gupta SK [58])

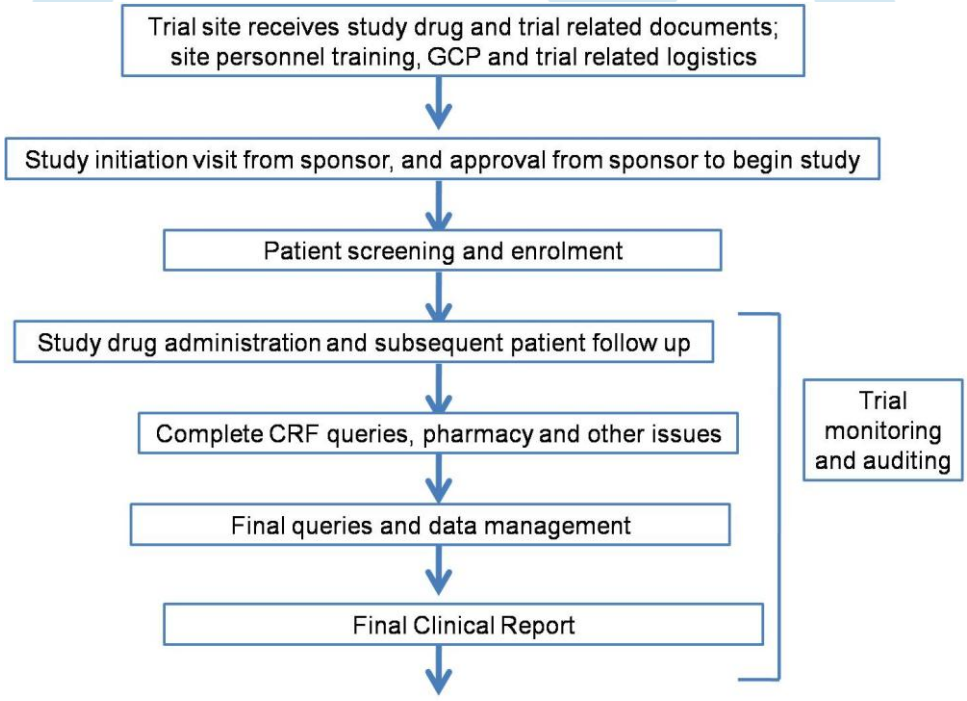

Figure 6: Ideal clinical trial operations process (Part 3 of flow chart) (Adopted from Gupta SK [58])

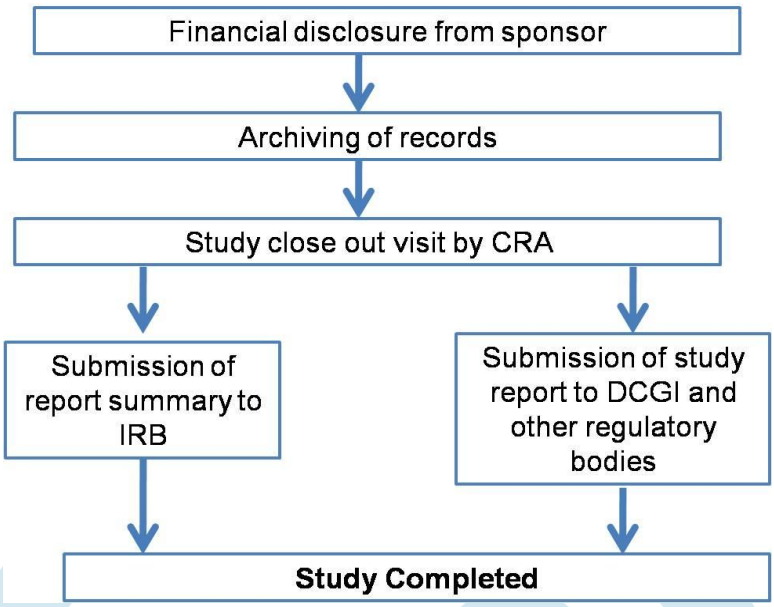

Figure 7: Ideal clinical trial operations process (Part 4 of flow chart) (Adopted from Gupta SK [58])

All of the above processes need to be conducted as per guidance provided by ICH GCP (ICH E6) [59] and respective regulation of that country.

Roles and responsibilities

Different stake holders that are involved in clinical trial process include sponsor, contract research organization, investigator, co-investigator, clinical research coordinator, institutional review board, clinical research associates, data management team, pharmacoviglance team, and regulatory authorities. Sponsor has ultimate ownership for investigational drug and is responsible to finance, maintain conduct, and conduct of audits at sites to ensure abidance with GCP and regulations. Investigator and co-investigators are medical professionals responsible for conduct of trial at site and they perform subject recruitment, retention, and trial conduction. Clinical research coordinator does working under investigator and helps him for smooth conduct of clinical trial. Institutional review board (IRB) is responsible to ensure well-being, rights, and safety of clinical trial participants at trial site. Monitor or clinical research associate (CRA) ensures conduct of trial at site by different visits such as site feasibility, site initiation, site monitoring, and site closeout visits. Clinical data management department is responsible for entering data, data review, data lock, and data analysis. Adverse effects of investigational drug are monitored by pharmacovigilance team. Signal detection, amplification and signal confirmation are done by pharmacovigilance team. Permission to conduct and approve clinical trial, meetings with sponsor to discuss the data and after phase III of clinical trial, marketing authorization is given by regulatory authority [59].

Types of studies [60]

Different authors have classified clinical trials into different ways. However, in general they can be divided into treatment (intervention) trials, prevention trials, observational trials, diagnostic trials and surgical trials. Treatment trials or intervention trials are type of trials in which objective is to investigate effectiveness of drug for treatment of particular disease. Treatment trials could be superiority, inferiority and equivalence trials. Prevention trials are aimed to identify ways to prevent particular disease causation or recurrence. Case report studies rank at the bottom and randomized controlled trials at top of hierarchy of clinical evidence. Observational trials include case control and cohort studies. In case control study, outcome cases (i.e. persons affected by disease) are compared with controls (i.e. disease free). As this design travels backward of time, it is also called as retrospective design. Cohort studies progress from exposure to outcome (hence called prospective). When compared to case control studies, cohort are easier to understand and conduct. Cohort studies are useful to determine incidence rates of adverse events and to evaluate risks. Another advantage of cohort study is single study may provide information of various outcome variables. For any study type, observational or experimental, study should have both internal and external validity. Internal validity provides unbiased estimate of measurement. External validity justifies that results from study can be generalized to population [61].

Clinical Trial related documents

Documentation is key thing for conduct and evaluation of clinical trial. Documents are generated in three stages in clinical research process:

1. Before the conduct of trial
2. During the conduct of trial
3. After conduct of trial

Documents that are necessary to be made before conduct of trial include protocol, investigator's brochure, informed consent, case report form, clinical trial agreements with investigator and sponsor, etc.

Case report form is unique document used during conduct of trial to note down protocol required data elements. Case report form is electronic or paper document aimed to collect information of data elements from protocol. In present day, electronic or paper formats of CRF are available. Properly designed CRF provides quality assurance of elements required by protocol ensures regulatory compliance and provides a means of collecting data. Electronic version of CRF has advantages over paper CRF as its less time consuming and reduces work of data entry and helps company to perform large multi-centric, multinational clinical trials5. Validated electronic CRFs are more accepted by regulatory authorities across globe. Also to note that eCRFs are easy for linking data, data cleaning is easy and quick. Pavlovic et al. [62] conducted study on paper and electronic data collection. This suggested that electronic data capture decreased costs by 55%. Jeannic et al. [63] conducted comparative study of both CRF formats by observing 27 studies in year 2001 to 2011. They suggested that both formats are advantageous in particular situations. eCRFs are helpful in large, low risk trials. Electronic version is preferred over globally by many sites and people working in these settings.

Clinical trial data management

After the conduct of clinical trial, data management plays important role to get results about effectiveness and safety of treatment. Data management program begins with data capture. In older days, data capture was done by manual data entry from case record form into computer systems. There are two types of data entry models: centralized and decentralized models. In most companies, data is entered into central location, and is called centralized data entry. In decentralized data entry, data is entered at investigator's sites or at local site offices. Centralized data entry is most preferred model as data is available in electronic systems and is thus easy to clean and analyze, so that conclusions can be obtained. In order to implement, this model, organizations generally employ data entry support staff to generate database. This model is dependent on certain factors such as support systems and software, maintenance, stability and security. Paper CRFs from different sites need to be couriered or mailed to central site locations. This causes time delay in data entry and increases costs. Use of scans or fax technology will overcome this delay [64].

Data validation means series of steps conducted by Sponsor Company that turns raw original data recorded in CRF into clean data. Data validation process starts right from investigator's site up to analysis and representation of data into final clinical study report. Right initiatives of data validation taken right from investigative site ensure quality of data submitted in NDA submission. This is ensured by right, appropriate and completely filled CRFs at site which are completed in timely manner. This is checked for errors by monitor of company. After this, CDM department does validation via pre-entry review, edit checks, data clarification, and database up-gradation steps, etc. These steps ensure quality of data and hence validated data is acceptable by regulatory authorities. However, data validation requires electronic data capture systems (EDC) if data validation is started from investigative sites, requires sophisticated computer software [64].

Implementation of computer systems and validation of them as per 21CFR part 11 provides paperless environment in company. Although paper based environment is preferred by people, it is flexible, easy to use; it is not suitable for long term period of time. Computer systems validation is acceptable is essential thing for pharmaceutical firms mandated by regulatory authorities such as US FDA and EMA. Implementation of this system provides regulatory compliance with GxP (manufacturing, clinical, laboratory, etc) guidelines. Uses of validated systems provide easy retrieval of database of a project leading to improvement in efficiency, productivity, and reduction in operating costs. Overall, it improves quality of process [65], [66].

Role of clinical / medical coding in data management

Clinical medical coding has immense important in coding of medical terms. This process provides linkage of identical or similar terms and thus provides fast, consistent and easy retrieval of information. It arranges terms in pyramidal manner with large terms at top and exact pinpointed terms at bottom. This process thus provides standardization in entire company or particular country's regulatory authority. Due to uniqueness of terms, it gives unique code that makes easier for reporting. In case of data management, coding provides recording and storage of terminologies into database; facilitates easy data search, manipulation and analysis; data can be presented in different formats; and provides reproducibility of data by providing uniformity in terminologies [67]. Different coding dictionaries such as World Health Organization – Adverse reaction terminology (WHO-ART) [68]; Coding System for a Thesaurus of Adverse Reaction Terms (COSTART) (which is now superseded by MedDRA) [69] and International Classification of Diseases (ICD) [70].

Audits

Audits are systematic and autonomous/independent examination of clinical trial activities. Audit activities help in identification of audit trail. It helps in assessment of conduct of activities, provides indication about quality of documentation standards implemented actually. It provides authorization of systems and acts as means of ensuring validation of quality systems implemented by company. Different types of audits such as investigator audits, data management audits, FDA/ regulatory audits, internal quality assurance audits help in determining conduct of clinical trial as per regulatory standards. US FDA has bioresearch monitoring program (BIMO) for conduct of audits. Inspectors are given compliance program guidance manuals (CPGM) so as to evaluate and conduct audit as per regulations [71]. In order to increase quality of data in clinical trial, US FDA has increased number of audits of sites up to 11 percent in year 2014 (i.e. 1136) from 2013 (i.e. 1019) [72].

VII. CONCLUSION

Drug discovery is tedious task that involves series of steps from target identification to end of phase III clinical research. Different techniques such as molecular modeling, 3D pharmacophore, conformational analysis, molecular superimposition techniques help in screening of lead molecules. Selected lead compounds are subjected to preclinical research. Pre clinical research in animals involves rodent and non rodent compounds. This program is done in both short term and long term basis depending on duration of clinical trial. After successful safety assessment, clinical trials are conducted in phase I, II and III. Data from clinical trials are entered, validated, coded and analyzed to obtain results. Successful approval of NDA is achieved through quality in clinical data management and conduction of clinical trial. Audits play important role in ensuring quality of clinical trial data.

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