ORIGINAL ARTICLE

Application of critical path analysis in clinical trials

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ABSTRACT

Clinical research operates in a strictly regulated environment under various management models, but a distinct management model of clinical trial (CT) still needs exploration and research. Critical path analysis (CPA) is a management approach can be used for monitoring, analysis, and prediction of success of its time-bound operational activities. A model CT was compiled with 78 activities, which were further merged into 35 major activities. After performing dependence analysis, the list was finalized with 25 activities which were taken in activity predecessor to create a network diagram and perform CPA considering patients, conduct, and outcome. Activities were inclusive, described the trial entirely with accuracy, and were in chronological and logical sequences. This approach does not replace an understanding of or adherence to the requirements contained in all applicable regulations, guidelines or standard operating procedures governing clinical studies but ensures the proper use of operational and decisional approaches including optimal resource management. As the need to meet deadlines becomes more important and the need to produce good, stable project plans, CPA is very useful for determining activities that can lead to project delay. With this approach, project may be effectively monitored, and realistic schedules can be maintained.

Key words: Clinical trial operation, critical path analysis in clinical trial, decision model in clinical trial

INTRODUCTION

Within clinical trials (CTs) there are three dimensions where activities, their duration, and the conditions on which these time-bound activities unfold decide the fate of the study. These are: (1) Assessment of safety – prediction if a potential medicinal product will have any safety concerns through the evaluation of its potential adverse effects, (2) proof of concept and large studies efficacy, (3) postmarketing surveillance, pharmacovigilance, and periodic safety update reports. The coordination of an individual CT project and the general management of the projects running simultaneously have a strategic importance to ensure timely marketing authorization of the promising candidates in the portfolio.[1-3] In all phases of CTs, the common management items tend to remain the same, i.e., the scope, resources, and the timelines.[4-6] The productivity of the pharmaceutical industry has decreased over time, and the costs of producing new medicines have been rising sharply.[7,8] Critical path analysis (CPA) is a method which is intended to improve drug development and reduce uncertainty and cost by applying scientific tools to the clinical development process.

When activity durations are deterministically or experientially known, the CPA can be applied to manage time and resources for a given trial.[9,10] The motivation for CPA and overall project management for CTs come from the fact that there are many dependent and

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independent (parallel) activities involved, and also there are many uncertainties. To meet the objective of systematic planning, the managements have evolved a number of techniques applying network strategy. CPA is one of the many network techniques which have been widely used for planning, scheduling and controlling the large and complex projects. CPA formally identifies tasks which must be completed on time for the timely completion of the whole project. It also identifies which tasks can be delayed if the resource needs to be reallocated to catch up on missed or overrunning tasks. A further benefit of CPA is that it helps us to identify the minimum length of time needed to complete a project. Where we need to run an accelerated project, it helps us to identify which project steps we should accelerate to complete the project within the available time. The disadvantage of CPA, if we use it as the technique by which our project plans are communicated and managed against, is that the relation of tasks to time is not as immediately obvious as with Gantt charts. This can make them more difficult to understand.[11,12]

CPA emphasizes on activities and not on uncertainties while estimating its activity times.[13-15] It is not always possible to sort out completely identifiable activities and their start and finish times. Time estimates have an element of subjectiveness in them. In this paper, we tried to design and develop an innovative CT management approach for a project-specific operating plan during the conduct of the study. This CT management approach does not replace an understanding of or adherence to the requirements contained in all applicable regulations, guidelines, or standard operating procedures governing these studies but ensures optimization of CT design, analysis, trial management, and cost.

RATIONAL METHODOLOGY, APPROACH, AND RESULTS

Initially, the activity list of a model CT was listed in different 78 activities, which was further merged into the major 35 activities. After further consideration and dependence analysis, it was finalized in the 25 activities which were taken in activity predecessor table for the purpose of network diagram and CPA considering patients, conduct and outcome [Table 1]. Activities are inclusive; describe the trial entirely with accuracy, in chronological and logical sequences. Dependency nature is both qualitative and quantitative [Table 2] and also validated by experts. Primary and secondary outcomes were appropriate, ethically approved, approved by the concerned regulatory agency, scientifically standardized as well as patients were well cared [Figure 1].

To determine the flow of these activities, we need to create a precedence diagram. Activities which must be completed before a particular activity starts are called predecessor activities, and those which must follow a particular activity are called successor activities. After deciding the precedence order, the activities are put in a logical sequence using the graphical notations. While constructing the network, to ensure that the activities fall

Table 1: These 25 activities were taken to create a network diagram and perform CPA considering patients, conduct, and outcome

A. Development of protocol and IB (draft preparation, review, finalization, and approval)
B. Development of CRF and ICF (designing, review, draft completion guidelines, and approval)
C. Develop outsourcing plan (business proposal, receive and evaluate, audit vendors, choose vendors, contract negotiation)
D. Development of drug supply management plan (request for IP formulation, drug labeling design, review/approval, printing, and preparation)
E. Set up database (validate DB, develop data quality, develop SAP, write analysis program)
F. Site identification and screening, telephonic feasibility and site selection screening, site selection visits planning/site visit confirmation, site selection visit and collection of site essential documents, finalization of SSV reports and finalization of qualified sites
G. Budget negotiation, CTA review by legal dpt. and final negotiate a contract
H. ICF translations, review, approval, translation certificate, study insurance certificate
I. DCGI submission and approval, CTAs signing by all the parties
J. CTRI registration, preparation of EC submission packets and allocation of sites to the CRA
K. EC approval
L. Study monitoring plan and approval; study travel plan preparation and approval
M. Required infrastructure at site and its approval
N. IM planning, IM presentation finalization, IM binder printing
O. SIV preparation, dispatch of IP and other site requirements, SIV
P. FSFV, enrolment timelines, enrolment of patients
Q. Conduct monitoring (SMV, Medical monitoring), corrective action plan review meeting
R. CRF retrieval
S. DM database designing, approval and data validation plan approval
T. Data entry, (double data entry) data validation, DCF generation, and tracking
U. LSLV
V. DCF resolution, data cleaning and database lock
W. SCOV, destroy or return of unused drug, (site close out)
X. Statistical analysis, CSR writing and final CSR
Y. Reconcile final records and close study and documents archival

IB: Investigator brochure, CRF: Case report form, ICF: Informed consent form, IP: Investigational product, DB: Database, SAP: Statistical analysis plan, SSV: Site selection visit, CTA: CT agreement, DCGI: Drug Controller General of India, CTRI: Clinical Trial Registry of India, EC, Clinical Research Associate, SIV: Site initiation visit, FSFV: First site first visit, SMV: Site monitoring visit, LSLV: Last site last visit, DCF: Data clarification form, SCOV: Site close out visit, CSR: Clinical study report, CT: Clinical trial, IM: Investigator meeting, DM: Data management

Table 2: Activity - predecessor relationship to describe how each activity is dependent or independent from another activity which precedes this given activity

Serial number	Activity	Predecessor
A	Development of protocol and IB	-
B	Development of CRF and ICF	A
C	Develop outsourcing plan	-
D	Drug supply management plan	A, B, C
E	Set up database	A, B
F	Selection of potential sites	A, B, C
G	Budget negotiation, CTA customization/review, and CTA review by legal department and final negotiate contract	F
H	ICF translations, review, approval, translation certificate, study insurance certificate	E, F
I	DCGI submission and approval, CTAs signing by all the parties	F, G, H
J	CTRI registration, preparation of EC submission packets and allocation of sites to the CRA	I
K	EC approval	J
L	Study monitoring plan preparation and approval and study travel plan preparation and approval	J, K
M	Quotation for required infrastructure at site and approval, procurement and infrastructure installation at sites	J, K, L
N	IM planning, IM presentation finalization, IM binder printing	I, K
O	SIV preparation, dispatch of IP and other site requirements, SIV	M, N
P	FSFV, enrolment timelines, enrolment of patients	O
Q	Conduct monitoring (SMV, Medical monitoring), corrective action plan review meeting	O, P
R	CRF retrieval	Q
S	DM database designing, approval and data validation plan approval	-
T	Data entry (double data entry), data validation, DCF generation and tracking	R
U	LSLV	T
V	DCF resolution, data cleaning and database lock	U
W	SCOV, destroy/return unused drug, site close out	V
X	Statistical analysis, CSR writing and final CSR	V
Y	Reconcile final records and close study and archival of documents	X

IB: Investigator brochure, CRF: Case report form, ICF: Informed consent form, CTAs: CT agreements, DCGI: Drug Controller General of India, CTRI: Clinical Trial Registry of India, EC: Ethics Committee, CRA: Clinical Research Associate, IM: Investigator meeting, IP: Investigational product, SIV: Site initiation visit, FSFV: First site first visit, SMV: Site monitoring visit, CRF: Case report form, DCF: Data clarification form, DM: Data management, LSLV: Last site last visit, DCF: Data clarification form, SCOV: Site close out visit, CSR: Clinical study report

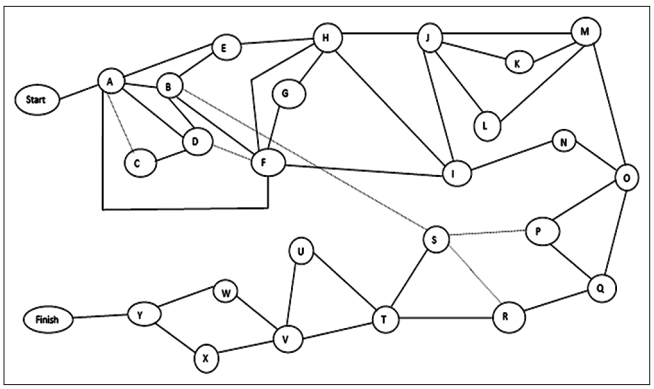

Figure 1: Network diagram based on the activity-predecessor table including activities from start to finish. In this figure, all 25 activities mentioned in Tables 1 and 2 were taken to design the network A–Y. The activities which were linked to another activity (ies) are connected with the direct line to show inter-dependent relationships

in a logical sequence, the following questions need to be answered: (1) What activities must be completed before a particular activity starts? (2) What activities follow this? (3) What activities must be performed concurrently with this?

Critical path analysis

A delay in any of the critical path activities will delay the entire project, regardless of whether the other project activities are completed on or before time. The act of determining the critical path is known as the CPA.[14,16] The precedence diagram shown in Figure 2 has multiple paths highlighted as the green line, red line. One of the paths in Figure 2 is the critical path.

Slack and float both refer to the amount of time by which a particular event or activity can be delayed without affecting the time schedule of the network. The total float of an activity is the difference of its latest start time and its earliest start time. The activities which have zero floats are critical activities and are on the path of critical activities, the critical path. Total float represents the time by which an activity can be delayed without affecting the project completion time.[17]

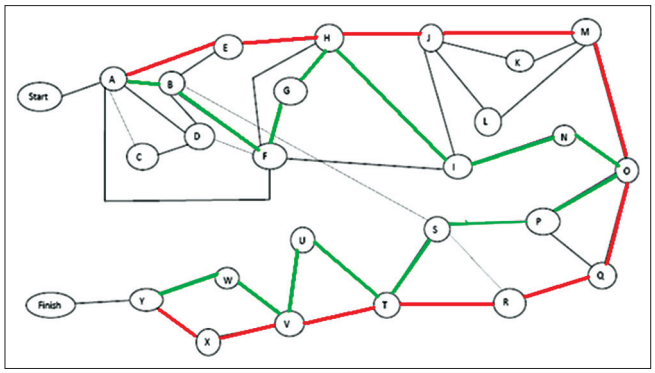

Figure 2: The red line of this diagram describes the critical path of the activities from the starting point to completion of a clinical trial. Please refer to Table 2 for the activities named A–Y

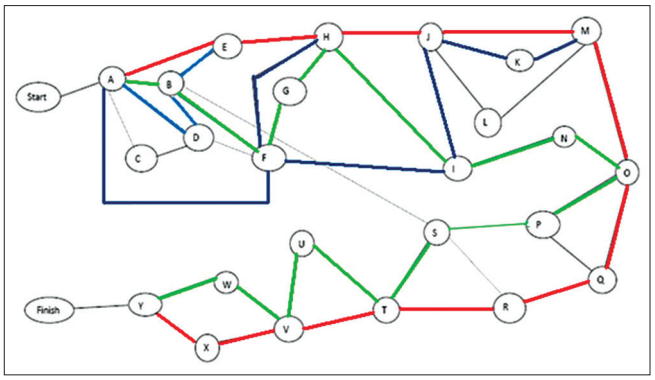

Figure 3: The diagram shown above describes the multiple paths highlighted with different colors with multiple activities and longest path that is, red lined path is the critical path of the project

In this network diagram, critical activities such as development of protocol and investigator brochure, informed consent form translations, review, approval, translation certificate, study insurance certificate, site initiation visit (SIV) preparation, dispatch of investigational product and other site requirements, SIV, data entry, data validation, data clarification form generation and tracking, reconcile final records, and close study plays vital role. Some of the noncritical activities of this project include development of drug supply management plan, Clinical Trial Registry of India registration, preparation of ethics committee submission packets, and allocation of sites to the Clinical Research Associate [Figure 3].

The longest path without any slack is the critical path. From the above diagram, we can see that path red lined is the longest as compared to green and blue lined path. Therefore, if activity on this path is delayed, then the project will be delayed. After identifying the critical path, we can deduce the activities that when delayed will not impact the project. Calculating the float of each activity using the CPA to determine the amount of time an activity may be late without delaying the project. The proof of concept application of CPA and related technique was corroborated.

DISCUSSION

By executing this approach repeatedly, an arbitrarily large number of realizations of project completion time may be generated allowing inference of its uncertainty. In addition, cost uncertainty with time-dependent effects can also be quantified by secondary calculations in the project network.[18] Some believe that a project plan is just a list of specific tasks and deliverables, organized across time and into larger groupings that begin and end with major project milestones.[19,20] However, a project plan is not just a timeline management but also achieving the objectives clearly and being answerable to stakeholders by managing well all sorts of resources.

Major factors in determining the success or failure of clinical development projects are how well the planning process is carried out, whether the clinical project managers are involved early enough to understand the product development goals, executive sponsorship, and stakeholder involvement. Senior level leadership in the planning phase is common in established pharmaceutical companies, but we recommend that the attention is given to developing strategic development plans also extend to individual clinical study plans. In smaller biopharmaceutical companies without dedicated project management offices, strategic product development planning conducted to satisfy investors usually lacks a rigorous operational component. In the absence of mid to senior management leadership, this planning is almost nonexistent, increasing the risks for each individual clinical study.[18,21] In the clinical research setting, a project is a unique CT. It has a discrete start date and end date. The project team works within a matrix reporting environment to ensure that the tasks required for completing the project are done within the project timeline and with the quality that meets or exceeds the client's expectations.[22] Within a Clinical Research Organization, project management can include satisfying the client, supporting the project team, and senior management. This is not an easy process. Most of the time, the project manager ends up sitting on a fence between what the client wants and what senior management wants. At the end of each day, the project manager must ensure that both sides are happy with the project's performance. Because the planning gap for clinical projects is persistent and widespread, managing each section of a typical project plan during the definition and planning stages is key to the success of the study.[23-25]

CONCLUSION

As the need to meet deadlines becomes more important, producing good and stable project plans become imperative. We can see that the critical path method or CPA is very useful for determining activities that can lead to project

delay. Based on actual results, resource reallocation can be considered for further better management of complex CTs. The management of CT resources can only be carried out effectively if a series of accurate resource models can be produced that can provide a range of project execution alternatives. In this way, the project may be effectively monitored, and realistic schedules can be maintained.

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Conflicts of interest

There are no conflicts of interest.

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