Approach to mitigate challenges in Clinical Trial Supply Management

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Abstract—Clinical trials in drug development involve producing, distributing and administering the candidate therapy to volunteer patients located in different geographic zones. The development activities required to bring a new drug to market involve considerable expense ($1+ Billion) and can take about ten years. Literature review suggests many approaches to reduce clinical trial costs, including innovations in trial organization and patient pool selection. Although several pharmaceutical companies use different Enterprise Resource Planning (ERP) packages for commercial supply chains they are often unable to effectively leverage it for Clinical Trial Supply Management (CTSM). Drug makers need an efficient supply chain with an effective IT infrastructure to meet their clinical trial goals. These may include accurate and timely supply of drugs to patient sites, at optimum cost while ensuring compliance with regulations and goods manufacturing practices. Presently clinical trials in supply chain have many challenges like Uncertain and frequently changing demand due to variation in patient enrolment/dropout rate, Lack of visibility at all points in the supply chain (e.g., patient trial sites) and High cost of operation, Specialized packaging and labeling requirements to facilitate randomization and blinding, Need for adherence to multiple regulations when manufacturing, distributing and conducting trials in different countries. Delay in decision-making due to lack of integration with contract research organizations (CROs) and site systems for end-to-end visibility of the supply chain, Delays in trials leading to expiration of drugs, relabeling, returns and remanufacturing, Lack of intuitive and user-friendly interfaces leading to organizational change management issues.

The objective of this paper is to present a comprehensive approach for development of integrated ERP application for CTSM solution to achieve the above challenges involved in the clinical trial supply chain. It is also proposed to study feasibility of making this CTSM solution available on cloud. It is expected that this approach will be able to give many benefits to overcome the challenges mentioned above.

Keywords—clinical trial, supply chain, CTSM, randomization, clinical trial challenges and clinical trial supply management.

I. INTRODUCTION

It is no secret that clinical development represents the longest and most cumbersome aspect of launching new drugs into the global marketplace. Product development challenges have increased due to increased regulatory requirements, new technologies, and the complexity of studies being conducted. One important factor in successfully conducting clinical studies is the efficient management of clinical trial supplies, particularly for those complex studies require detailed monitoring, precise planning and coordination between many players.

Research recently conducted a benchmarking study on the clinical supply chain. This highlighted the increasingly complex environment in which life sciences companies are working. To thrive in this environment, companies need to become globally agile enterprises, and this requires a more effective and efficient supply chain than currently exists. However, the focus needs to expand beyond the commercial supply chain to encompass the clinical supply chain. Only then will companies achieve their goals of reducing time to market, shortening study timelines and reducing R&D costs.

Inefficient clinical supply chains will increasingly put these complex global trials at risk. The success of these studies is heavily dependent on providing study supplies to often large numbers of sites so that drugs can be administered at the correct times throughout the study. Issues such as supply stock-outs can result in patients being disqualified, potentially jeopardizing the entire study. However, forecasting of trial stock requirements is difficult, particularly with the rise of adaptive trials. Patient recruitment occurs at different speeds and patients sometimes drop out of trials before study completion.

Integrated comprehensive CTSM solution is a need of an hour to manage clinical trial supply and that too at a low operational cost. The solution need to cater all the above mentioned functionalities and their integration aspects from clinical trial supply point of view.

II. CHALLENGES

Although several pharmaceutical companies use ERP for commercial supply chains, they are often unable to effectively leverage it for CTSM. Drug makers need an efficient supply chain with an effective IT infrastructure to meet their clinical trial goals. These may include accurate and timely supply of drugs to patient sites, at optimum cost
while ensuring compliance with regulations and Good Manufacturing Practices (GMP).

There are several loose ends in the existing solutions available in the market, which meet the challenges of clinical trial supply management at higher cost. Various solutions are available in the market however those do not provide integrated, comprehensive end to end solution for clinical trial supply management starting from R&D processes to the supplying drugs to the patients, undergoing clinical trials. Also integration of enrolling patients, collecting patient data before and after trials, slicing and dicing of data from clinical trial studies conducted, forecasting of drug dosages at various sites, simplification of processes relevant to regulatory submission, handling country specific labelling management and batch traceability.

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III. OBJECTIVE

Comprehensive on premise ERP based CTSM solution addresses the unique challenges involved in the clinical trial supply chain. The CTSM solution can be made available on the cloud with a specific focus on the mid-market segment and contract research organizations (CROs). This solution can be on in memory computing database for enhanced performance due to in memory computing and tighter integration between suppliers and customers. Cloud enables agility and cost optimization while maintaining the best-in-class features of the highly scalable on premise solution. Solution offers in built forecast and planning, Randomization, shelf life expiry calculation and also is scalable to integrate further patient management systems. Global Label templates can be defined further or has scalability to integrate with Global Label Management system.

Key objectives of this Comprehensive Integrated CTSM solution are

Clinical Data Management - Create and update (manually and / or automatically via an interface) clinical study master data while providing a single source of information to all business units on the clinical under way

Forecasting and Planning – Calculate enrollments or demand for different delivery units / pack types at each trial site

Randomization - Create and manage randomized lists and allocate medication numbers to packaging process orders for follow-on packaging and label printing

Clinical Packaging and Distribution - Create hierarchical packaging of MediKits, boxes and pallets with unique sequence numbers and print barcoded labels for delivery units Enable industry specific medication number allocation to both supply and replenishment deliveries

Clinical Projects Planning and Budgeting - Capture all scheduled activities for a project using Project Planning, a powerful tool, together with planned costs and material with a hierarchy of work breakdown structure (WBS) as required

Intuitive User Interface - Perform key business functions on screen with intuitive and user-friendly interface for extensive adoption of the solution and user satisfaction

Mobile-Enabled Transactions - Enable real-time data entry for faster decision making by allowing remote access to transactions

IV. RELATED WORK

The clinical development phase is the longest and most expensive part of bringing a new drug or medical device to market. Efficient management of clinical study supplies across the supply chain along with precise planning and coordination of activities, both within and outside the organization, are key to successfully conducting clinical studies.

To overcome the above mentioned challenges in introduction and Literature review chapters; An comprehensive and end to end ERP based customized solutions is developed on database (In memory computing). This solutions has almost all futures mentioned in the objective of the projects and few are in developments stage. This solution has several modules like Forecasting and Planning, Randomization, Manufacturing and Warehouse management, Label Management, Shelf life tracking of batch, Distribution of drugs etc. User Intuitive interfaces are built to enhance user experience and increase efficiency of user eventually increasing productivity. Solutions can also be hosted on Cloud and can be packaged as per the need of size of business being operated.

A. Architecture of Clinical Trial Supply Management

B. Key Highlights and Features of the Solution
- Seamless integration and collaboration: Enhance data collection between multiple agencies by simultaneous upload and access information.
- Centralized Systems: Allow access to systems/application from any local time at any time.
- Data collections and management: Enables faster data collection and consolidation for rapid transmission to different sites globally.
- Multi-level warehouse management
- Study and forecasting characteristics
- Packaging and randomization management
- Interactive Response (Voice and Web) patient management CTMS integration
- Clinical order management
- Label print launch management (Global Label Templates)
- Clinical batch management and country approval
- Clinical expiry date and shelf life management
- Clinical master data management
- Packaging electronic batch record

C. Clinical Forecasting & Planning
Before a trial begins, forecasting needs to be made: the amount of new investigational medical drug is required for a set of patient across the length of clinical development program?
For short term planning, basic algorithms, the number of investigative sites x the number of patients per site x dosage of patients x the period of the trial, can be used to provide a study forecast. However, when the trial begins, a range of factors inevitably alter these original forecasts and impact planning. Three key factors include: Patient recruitment, Expiration dating, Integration across all manufacturing steps and Distribution.
Forecasting in CTSM may take place at a DS (Drug Substance), DP (Drug Product) or a Patient Kit – CFGs (Clinically Finished Goods) level. Long term forecast covers all demands within a longer time period (i.e.1-3 years) to plan already very early the replenishment of critical raw materials and capacity availability. A development pipeline is typically being filled from bottom up, starting with DS. In mid-term forecasting, the drug product and drug substance demand quantities will gain more granularity.

D. Multi Level Packaging
Randomization and Blinding: Randomization in clinical trials is the process of assigning participants to different treatment groups in random sequence. Randomization gives each participant in trial an equal chance of being allocated one of the trial groups. Group allocation must be unpredictable for successful randomization.

Single Blinded Randomization tool
Double Blinded Randomization tool
Triple Blinded Randomization tool
Non Blind or Open Label Trial Randomization tool

In Randomized control trial, patients are first assessed for eligibility and recruitment and then are randomly allocated to receive a type if treatment from various alternative treatments under study. Random allocation in a real trial is complex and is managed under a randomization tool.

At the end of the clinical trial, differences occur in outcomes between two treatment groups, following logic may be considered for randomization
Simple Randomization- Patients are randomly allocated for trials without considering any factor.
Stratified Randomization – Patients being divided in two or more specific groups on the basis of few predefined factors like male over 75, male under 75, Women over 65 etc.
Factorial Randomization – Two or more factors are being considered for grouping of patients.
Randomization: During Multi-Level packaging process, drugs are assigned a random number, which is printed on the packaging label. The label also contains details like protocol id and batch details (e.g. shelf life expiration date).

In case of clinical trials for single blind and double blinks of trial, it is necessary that primary packaging of the drugs looks identical for drugs belonging to different pack types (secondary packaging). The label printed on this kits is identical hence helps to maintain uniformity during secondary packaging for drugs of different pack types. A random number list is generated from a tool or updated manually. These numbers are assigned to the drugs belonging to various pack types (active, placebo etc.)

In Single Blind types of clinical trial, the medication dispensed to the patient is blinded from the patient, but the clinical site personnel is aware of the medication that is being dispensed.

The patient and the clinical site personnel are both aware of the medication that is being dispensed in the Open Label types of trial. The medication dispensed to the patient is blinded to both the patient and the clinical site personnel in double blind.

E. Warehouse Management

Warehouse management in CTSM solution is use to develop a global platform in Drug supply to clinical trials in order to achieve visibility, ensure on-time value adding sourcing inputs and performance measurement. Warehouse management executes and manages inventory activities. WM integrates very tightly with other ERP modules; processing requests for inventory, and managing both the inventory retrieval and inventory put away activities.

WM is the function in an organization that is responsible for following business processes. Receive materials from supplies and goods from production. Store material under the most appropriate conditions and Prepare materials for process orders. Transport material into Production staging area and prepare goods for shipment. Keep inventory books accurate and report stock levels and transactions.

F. Label Management

The labels for Clinical Finished Goods (CFGs) can be printed in-house within ERP System. A print order is created including the ERP packaging/process order, number of labels, components and (external) label ID(s). ERP print order allows to create label control report. The barcodes are generated and maintained within ERP. The ERP print request are directly linked to external print request of External Labelling System.

G. Distribution

Distribution Process in the CTSM solution deals with the supply of clinical finished goods within the organization as well as to the 3rd party customers (Clinical Trial Sites).

Distribution process in CTSM solution are broadly classified into two processes.

Depot Replenishment Process: This process deals with the replenishment of stock at depot (regional hubs) from clinical packaging site. This is done through stock transfer order.

Depot to Site Process: This process deals with the shipment of Medi Kits (CFGs) from depot (Regional hubs) to clinical trial sites. This is done through sales order.

Distribution process is integrated with warehouse management module to achieve visibility, ensure on-time value-adding sourcing inputs and improve performance measurement.

Distribution process in CTSM solution has functionalities like batch search help for the STO and sales order, serial number assignment for STO and sales order, creation of sales order with the unique combination of study code/protocol ID and serial number and picking and goods issue with RF scanner.

H. Intuitive and User Friendly Interfaces and Mobile Enabled Transactions

Key business function of based screen with intuitive user-friendly interface are developed for extensive adoption of the solution and user satisfaction. Also real time data entry for faster decision making by allowing remote access to transactions.

I. Conclusion and Recommendations

A significant opportunity exists for Life Sciences companies to improve the efficiency and cost effectiveness of their clinical trial supply chains. In the most successful cases, companies have started with a solid foundation – including a clear vision and a solid business case. They have introduced a comprehensive program – based on ERP technology, and supported by a change management program and organizational transformation.

An ERP system with processes based on supply chain best practices and enhanced to handle the intricacies of clinical trials will increase the effectiveness and efficiency of the clinical trial organization resulting in reduced time to market, shortened study timelines and reduced R&D costs.

Standard ERP processes for Life Sciences companies can be leveraged to a certain extent and can help to enforce “Supply Chain” thinking e.g., packaging and distribution should not be isolated processes as is the case at many organizations. However specific ERP clinical trials supply management functionality is still required to create a complete solution. This integrated CTSM solution on Cloud has following features and are implemented in the current scope of the project.

Integrated CTSM is Cost effective solution - due to modular nature of the solution, pre-configured and Cloud based solution. This would help to have a Productive partnership with CRO due to better integration between pharmaceutical and CRO systems to ensure:
• Supply chain agility
• Visibility in E2E supply chain
• Overall clinical trial process efficiency

This will provide faster realization of ROI with less TCO. This is simple and has intuitive user interface and also Mobile enabled business transaction.

**Future work**

Integrated CTSM cloud based solution having its own advantages over existing standalone CTSM solutions. However this project can be enhanced further as a future work as follows.

Randomization Algorithms Can be built in the existing solution to avoid interfaces with different Randomization standalone applications

Global Label management module can be implemented to take care of different global labeling and external integration with third party system can be avoided

Integration with patient management system needs to be established to capture patient enrollment data and analysis data for the trial being conducted on.

Pay-per-use model - Pay only for what you use with zero investment in on-premise infrastructure

Clinical data management to Create and update (manually and / or automatically via an interface) clinical study master data while providing a single source of information to all business units on the clinical under way

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