TOWARDS PHARMA 4.0 IN CLINICAL TRIALS: A FUTURE-ORIENTED PERSPECTIVE

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Teaser: This review highlights the key technology-related enablers in revolutionizing drug development (Pharma4.0) in clinical trials

Highlights

- A perspectival cyber physical-based framework for Pharma4.0 is developed

Abstract

Pharma4.0, analogous to Industry4.0, intended to transform the traditional drug discovery and development approach to help it to align product quality with less time to market, and create intelligent stakeholder networks with effective collaboration. Pharma4.0's pervasiveness has produced several conceptualizations, which have, however, led to a lack of clarity and definition. The main emphasis of this paper is falling into the clinical trial stage of drug development in the Pharma4.0 era. It highlights the current merged computerized technologies in clinical research and, proposes a perspectival Pharma4.0 framework for integrating these technologies. The impact and barriers of employing the proposed framework are discussed with the potential elucidations and some future-oriented research works are highlighted.

Keywords: Industry 4.0, Pharma 4.0, clinical trials, Artificial intelligence, Drug development

Introduction

Drug Development (DD) is an attempt for bringing a new pharmaceutical drug to the market once a lead compound has been identified through the process of drug discovery until manufacturing. It includes design and discovery, preclinical research, filing for regulatory status, conducting Clinical Trials (CTs) in humans, obtaining regulatory approval, and manufacturing to market [1]. DD is a lengthy, complex, and costly process, entrenched with a high degree of uncertainty that a drug will succeed. While new technologies have multiplied opportunities for process improvements, regulatory oversight has slowed adoption relative to other industries [2]. The CTs is a phase of DD that perfume research studies to evaluate the safety and efficacy impacts of medical intervention in people. Almost half of DD time and cost is expended on CTs [3].

Industry4.0 is the current trend of automation to have intelligent, autonomous, and decentralized ecosystems able to provide smart and integrated products and services by employing merging

technologies such as the Internet of Things (IoT), Cloud Computing (CC), and Artificial Intelligent (AI), Cyber-Physical Technology (CPT)[4], and blockchain technology. In the Industry4.0 era, blockchain technology brings transparency, security, cost reduction, and traceability to the ecosystem [5-6]. CC is the on-demand availability of computing power and data storage [7]. AI is a computational analytical approach to emulate human cognition, interpretation, and comprehension of complicated data [8]. CPT is a technology that uses IoT to integrate smart devices with a computational unit that hosts AI tools and is deployed on the cloud, aiming to monitor and control the physical processes [9]. In the healthcare system, these technologies provide significant contributions. Just as examples, IoT connects the employed smart and wearable devices to address some healthcare issues such as disease detection, patient monitoring, hospital operation management, and interoperability. CC can facilitate data accessibility and can boost collaboration levels among the medical teams, and researchers in a scalable and secure affordably. AI is employed to predict a quantity as a decision support system in many healthcare contexts such as medical imaging, screening, psychiatry, primary care, telemedicine, disease diagnosis, treatment, and drug discovery/developments. In addition, it simplifies the lives of patients, physicians, and hospital administrators by performing tasks that are typically done by humans. CPT can realize a health monitoring and control system that follows up the objects in the view area, sends the information to the AI tools located in the cloud, and handle and track any unexpected event more intelligently.

Pharma4.0 is the term for adapting Industry4.0 related technologies to DD aiming to promote the productivity of medical development processes with less time/cost and high quality. Recently Pharma4.0 related studies have been reported by some international pharmaceutical institutions, researchers, and industrial companies [10]. Most of these attempts focused on drug manufacturing. As an example, a cyber-physical-based PAT framework for Pharma4.0 was developed for drug manufacturing by Barenji et al [11]. As long as the author's knowledge in this context there is not any report on Pharma4.0 adaptation in clinical trials of drug development. This paper aims to review merging technology related literature (e.g. AI, Machine Learning (ML), Deep Learning (DL), IoT, CC, and CPT) to extract their potential fruits, applications, and capabilities in clinical research, and to identify the main enablers of the next drug development revolution. Then overlapping all enabler technologies by proposing an integral Pharma4.0 perspectival framework for CTs.

Summary of the related works

Initial search for relative keywords resulted in more than 226 researches in some databases such as Web of Science, PubMed, Scopus, and Google Scholar. By scanning the abstracts, 56 papers were relevant, and in line with the objective of our research. These papers were all read and related contributions were identified to highlight the required technologies, entities, services, and resources in CTs as will be described in the next sections.

Artificial intelligence in clinical research: time for context

Recently AI has been used in some clinical researches and trials for improving the safety, quality, efficacy, cost, and time to market of a potential new drug. Helgeson et.al based on the analysis of structured and unstructured data from a patient's Electronic Medical Record (EMR) besides protocol eligibility criteria used IBM Watson to determine the suitability of the patients to the CTs [12]. Table 1 represents some of the recent studies for predicting the outcomes and pharmacovigilance studies in clinical research. As reported in the table the authors used different AI methods and tools to predict an outcome or estimate enabler quantities based on input data such as Electronic Health Record (EHR) and EMR. A DL method, proposed by Wang et.al predicted the chronological age using vital signs and lab tests of EMR [13]. Walsh et.al [14], Shameer et.al [15], and Wong et.al [16] based on EHR and EMR used ML to foresee suicide attempts, readmission probabilities, and incident delirium risk respectively. Yang et.al used convolutional neural networks to anticipate disease diagnoses based on high-level semantic information of EMRs [17]. In a study, Avati et.al used DL and EHR to prevent over-estimating prognoses by physicians and mismatching of patient's wishes and actual care at the end of life [18]. AI is also used in many pharmacovigilance studies [19-21].

Improving on the current state of the art of using Embedded Tools and Devices in clinical research

Nowadays, clinicians attempt to use different Embedded Tools and Devices (ETDs) in different medical fields such as; medical scanning, pathology, dermatology, ophthalmology, cardiology, endoscopy, and vital signs [44]. An ETD is a context-aware tool or physical device that can perform computation and can connect with other ETDs. Different types of wearable biosensors such as neural implants (e.g. retinal stimulation electrodes [45], ECoG electrodes [i], artificial dermal sensors [46], electroceuticals [ii]), tattoo sensors (e.g. smart contact lenses [iii], electrochemical tattoo batteries, always-on EEG electrode tattoos [47], low-cost integrated circuit patches [48]) and molecular sensors (e.g. nano and microfluidic sensors, portable DNA sequencers, smart pills, nanobiosensors, functionalized nanoparticles [49, 50]) are some examples of EDTs that can gather the information about their environment at any given time and adapt behaviours accordingly [51].

Some ETDs may have a diagnostic performance that is comparable with medical experts, especially in image recognition-related fields [52]. It is reported by Komorowski et.al that the selected treatment by the ETD is on average higher reliable than human clinicians [30]. ETD can be used to implement automatic, real-time analytics technology and patient monitoring in some CTs like neurological disorders, epileptic, and depressive events in which patients' self-monitoring is almost impossible and the diagnostic profile of the patient is very specific. ETDs also have been used for automatic detection of cognitive and emotional states, patient monitoring in Parkinson's disease trials, and quality of sleep assessment in neurology trials [52]. ETDs have been used by Labovitz et.al to measure and increase medication adherence in stroke patients on anticoagulation therapy [53]. Gayvert et.al employed ETD to integrate the properties of a compound's targets and its structure to predict the likelihood of toxicity in CTs [54]. ETD has the potential to support healthcare by enabling self-monitoring of personal

activity, identifying patterns of behavior; and supporting communications with healthcare providers [55]. Table 2 summarized some of the recent applications of ETDs in clinical research. Furthermore, ETD can free up the skilled laboratory workforce for more demanding tasks that better use their competencies and it contributes to improving productivity, quality, and patient safety [56].

Despite the many benefits which AI and ETD employment in clinical trials may gain, from cost, and time reductions to quality and safety improvements, there are a lot of challenges that must address in using these technologies.

- The processing power of these tools is restricted to the users' local processor (e.g. edge computing, embedded device) and the potential use of CC in these tools may improve the quality of the results and time reduction.
- Commonly these tools are not connected that may limit their negotiation capabilities. IoT technology may boost the connectivity level and provides a universal pool of data exchange among all the tools involved in CTs.
- The learning capability of the tools is restricted since they have access to a limited amount of data and also they are embedded with one or a few AI methods for decision making. Employing IoT may upgrade the data accessibility level of the tools from local into big data. Moreover, a cloud that simultaneously hosts many AI methods improves the analytical, learning, and training power.

From system-level points of view; CTs commonly suffers from proper data exchange, integration, and acquisition among the involved entities since they are geographically distributed and heterogeneous in terms of operating and data management systems. Stakeholders' diversity may increase the possibility of data shrinkage in a project. Moreover, the existing CT data providers such as; ISRCTN registry, the International CTs Registry Platform (ICTRP), and clinicalTrials.gov are working autonomously and disconnected which may make knowledge accessibility difficult to the knowledge consumers.

Steinwandter et.al on the way to Pharma4.0 provided a review on current data science applications at various stages of the bioprocess life cycle [67]. A review by [68] and [69] explains the impact of data analytics technology, cyber physic systems, digitalization, industry 4.0, AI, digital twins, and continuous manufacturing on Pharma 4.0.

Development of Pharma4.0 perspectival framework: robust collaboration in clinical trials

Figure 1 presented Pharma4.0 clinical trials perspectival framework. Pharma4.0's perspectival framework for CTs is a platform for integrating all entities, resources, and services using cyber-physical technology. It denotes their structures and interrelations aiming to highlight the shortcomings, limitations, and weaknesses of the conventional CT approaches for possible academic and industrial improvements. Conventional CT approaches are enriched with CPT in this framework since it is foreseen that the planning, conducting, monitoring, and controlling of the trials are performed autonomously.

In the framework, an entity is an independent company or organization with whom each of those provides/requests services for the CTs that are interrelated to each other to grasp the goal of the project. For each project, the entities are categorized as core and supportive. A core entity has the main role in the project and those entities who have an auxiliary role are called supportive. As represented in figure 1, core entities are sponsors, Clinical Research Organizations (CROs), Cloud-based Computational Unit (CBCU), regulating authorities, and ethic committees. The supportive entities are data providers, and services companies (i.e. third parties).

Contrary to the conventional CTs procedures that sponsor took on the core burden of the project and act as the main enabler, in this framework, CBCU provides/requests services to/from all the involved entities aiming to facilitate the trails, improve the quality, safety, time and cost, and document visibility and reliability. CBCU improves the planning, conducting, monitoring, and controlling processes of the CTs and shares all the processed information with the corresponding entity(s) for further required actions. This entity employs a wide type of AI methods and tools for decision-making to improve the quality, safety, productivity, and effectiveness of the trails.

A CTs project will be started by a collaboration opportunity that is usually provided by the sponsor(s). This opportunity should be forwarded to CBCU for planning, then this entity will propose plans to the sponsor using AI. For preparing the project plan CBCU may make a connection with some supportive entities and the control strategies of a trial should be performed according to the sponsor's advice and supervision. As soon as a plan is prepared the sponsor will ask the CROs to conduct the trials and the CBCU will start to monitor and control the project. CBCU delivers quality and process-related information to the regulating authority before, during and end of the project and enjoys their supervisory services.

The involved entities provide/request a particular type of service from CBCU. To perform the assigned services, the CBCU may get services from other entities. The collective services provided by the entities are vital for the successful completion of the CTs. The sponsor is in charge of managing the interactions among the entities and acts as the coordinator to boost collaboration based on CBCU recommendations. CROs conduct the trials and provides patient, equipment, and researcher-related data to the CBCU using in-line, at-line, on-line, and off-line monitoring methods. The involved patients, researchers, and equipment of the entity also receive control and adaptation recommendations from the CBCU for possible improvements of patient safety, quality, and productivity of trials. Regulatory authorities and the ethics committee provide supervisory services to the project through the CBCU. Unlike conventional methods of supervision, in this framework, the supervision services are continues not discrete.

Lots of ETDs may employ in the framework by different entities. All these ETDs should have decision-making, negotiation, and connectivity capabilities. CBCU as the heart of the framework hosts lots of AI methods and tools that are deployed on the cloud. As a fact, all the connected computers, wearable smart devices, cell phones, and smart equipment like imaging, diagnostic,

analytical, portable monitoring devices are the project ETDs that are connected to the CBCU using IoT through the internet. A wide type of sensors may be used for data acquisition and monitoring applications in the framework. The generated data by these sensors may locally be processed by ETDs or forwarded to the CBCU for process on the cloud. Three groups of ETDs are considered in the framework including; patients, researchers, and equipment. A patient's ETD monitors the progress of a person through the provision of care during the trial. A researcher uses ETD to monitor the status of the equipment and patients and to receive trial-related information, commends, and guidance from the CBCU. Equipment's ETDs are for the systematic process of collecting, analysing, and using the information to track and monitor the equipment's progress. It also for measurement and evaluation of equipment status and control them following the plan which has been provided by CBCU. To evaluate and ensure the quality of in-processes and trial results Real Time Release Testing (RTRT) system is also considered.

Two main types of services can be performed by CBCU; clinical trial planning and clinical trial control. Each of these services holds some sub-services in a way that they should wrap the project goal up. The initial protocol of a CTs project should be provided by the sponsor(s) to the CBCU. The protocol is forwarded to the clinical trials planning unit, where the unit first demands project-related information from internal and external (i.e. clinical trials data providers) data storage systems and then processed the data in different domains and studies.

CTs planning provides wide types of services for the design and planning stage of the project. Some of the services are demanded before conducting the experiments while some others may be required during the project life cycle. CTs planning can provide outcome estimations, Quality by Design (QbD), CROs selection, patient selection/recruitment, pharmacovigilance, method design, protocol design & development, and data analytics sub-services. While all the sub-services are required for initialization of the project; QbD, CROs selection, method design, and data analytics sub-services are working during the project (i.e. dynamic planning) conduction and updates the findings till the end of the project.

As shown in figure 2a, the sponsor before starting the project requests the project-related outcomes estimations and pharmacovigilance studies reports from the CBCU. As soon as the sponsor decides to run CTs, a request should be sent to the QbD service provider to achieve the control strategies to perform the trials. This provider employs a risk assessment actor to find critical quality attributes and uses protocol actor to acquire the control strategies aiming to minimize the risks of the trials and improve safety. The developed control strategies will be used by the method and experiment actors to determine the most appropriate method and also to adaptively designing the experiments that will be returned to the sponsor. The sponsor uses an experimental plan to partner selection providers where this provider uses CROs and patient selection actors to select the most suitable partners. It is the sponsors' responsibility to ask the trial documentation actor to prepare and store the project reports and forward them all to the control protocol actor to translate the document into machine language

(B2B). Finally, the results of the study are forwarded to the sponsor for further decision making and a trial document will be prepared and stored on the internal data storage system. It is the sponsor's obligation to start or abundant the trial's conduction.

In case a plan is accepted by a sponsor, the final protocols for starting the trials will be generated by CBCU and forwarded to the clinical trials control unit. This unit is responsible to allocate the trails to the involved CROs and collects generated real data from the ETDs. As shown in figure 2b, monitoring and control actions can be realized by the CTs control unit. For monitoring, the trace data from the involved ETDs in CROs should be stored on an internal data storage system and then be used by patient and resource monitoring actors. The outcomes of patient monitoring are forwarded to patient safety actors for further safety action. The generated and monitored data is shared with all entities. The periods of performing monitoring actions are in accordance with the project's final protocol that is achieved by the planning unit. The control action is performed based on monitored data from the involved ETDs. This data is used for controlling involved ETDs and improving the management and integration level of the project. The control actor use monitored data and the final protocols to forward control commends to the ETDs. Depends on the type of the employed resource the comments might appear as an order (e.g. an order comes to a researcher smartwatch) or as a control signal (e.g. drop rotational speed of the motor to 1100 RPM).

Some of the plans in clinical trials may require updates during the project conduction based on the results of the performed experiments and generated data by the resources. The monitored data will be shared by the clinical planning unit for possible upgrades on the plan stepwise. As soon as a plan is updated the trial documentation and final protocols of the project will be upgraded in the data storage system. The monitored data also will be used by the CTs control unit to improve patient safety and acts as input data for the patient support system. During the conduction of the trial, the CBCU periodically prepares summary reports. These reports will be stored on the data storage of the system and may share with authorities.

Future landscape: challenges, and requirements

Pharma4.0 is not a single technology, but rather a collection of them. Undoubtedly, Pharma4.0 is revolutionizing the way of operation of the pharma and biotechnology companies in drug development. As illustrated in Figure 3, we foresee a possible impact of Pharma4.0 on three key contributors on clinical trials (i.e. sponsors, CROs, and regulators) and "data" as the main integrator. Every phase of CTs has four steps including design and planning, trial accomplishment, analysis and assessment, and reporting and dissemination. The impact of the paradigm in each of these steps is represented by arrows. While some of the impacts are on only one particular step some others may have an impact during project conduction. The paradigm may assist the workforces in performing the assigned tasks by providing real-time task-related recommendations. It may also act as a platform to boost the knowledge of the involved workforce and clinicians on an executive way of training. The sponsor is one of the lucky users of Pharma4.0 in CTs. The real data provided by the ETDs might

facilitate the selection, engagement, cohort, and recruitment processes of the patients with higher sensitivity. The CBCU delivers cross-computation services for the estimation of outcome using AI as well as real-time big data, this might promote discrimination and calibration process for verifying the performance of predictive models. One of the main gains of Pharma4.0 adoption is the integration of the generated data with the project workflows that might facilitate the administrative procedures of the sponsors and CROs and acts as an awareness system for project completion and endpoint detection. Pharma4.0 adoption might also smooth some of the responsibilities of the CROs. The real-time big data provided by the ETDs and the cross-computational services of the CBCU might improve the quality of diagnosis and treatment protocols and might facilitate patient monitoring, adherence, and retention processes. CBCU continuously collected the process data and provides comments to the ETDs that potentially promote its efficiency. Based on processed data, CBCU might recommend a new configuration for the heath space during trials. In the Pharma4.0 era, the regulators will be able to supervise the contributors in a real-time manner at any step of the project through CBCU. The ethical and safety concerns of the patients potentially will be well addressed since the regulators will have access to a more wide range of involved patient's related data. The truthfulness of pharmacovigilance studies might be improved since the regulators will have the chance to consider all the project-related data through the CBCU with less approval process time.

In Pharma4.0 the real-time big data of the workforces, clinicians, researchers, patients, and equipment is acquired from the ETDs and forwarded to the CBCU for analysis, standardization, and integration. The patient-related data is store as EMR and EHR on internal databases and might be shared with external data storage systems through the CBCU. All these might improve the data sharing and integrity level of the project. All the above-mentioned impacts of using the Pharma4.0 paradigm in CTs will assist the pharma and biotechnology companies to develop higher-quality drug products with less time to market and R&D investment with a higher level of patient protection.

Despite the widespread adoption and rave use of AI and ETDs in CTs, there are still several barriers to entry Pharma4.0. The most common Pharma4.0 adoption pitfalls can be related and rooted in resistance from personnel and patients, reluctance to fully adopt by the organizations, reliable physical and digital infrastructures and equipment, and regulatory barriers. Pharma4.0 adoption might be a concern to the researchers that their responsibilities will shift, or worse, that their skills will no longer be needed, and they will lose their job. The solution is to ensure there should be constant communication with researchers throughout the entire Pharma4.0 transition. This communication should include what is expected from them during the transition and what they can expect their role to be once the project is completed. Moreover, there can be a lot of hesitancy by the patients since many patients are concerned that their data unduly might disclose and their privacy does not protect. To address this need, CROs must focus on informing the participants on their rights (i.e. informed consent) and they must reflect the approaches used to data privacy and protection. Pharma and biotechnology companies as well as regulating agencies may be reluctant to adopt Pharma4.0 since it

might be a poor fit with the existing organizational structure. Besides, change may be hindered by conflicts between the ability of management to maintain coherent integration throughout an enterprise and the need for rapid deployment of the context in a more localized setting. One way to avoid this is; to run the paradigm in a selected pilot laboratory or department for a while to assess the performance and compare it with the current system.

The following are some of the future research directions on the Pharma4.0 framework.

- Simulation platforms should be used to test and validate the developed framework.
- Empirical pilot studies for justifying the developed framework should be conducted on different levels of abstractions such as process and project levels.
- A QbD based patient safety system can be adapted with the framework to boost the quality of the project.
- Blockchain technology can be used in the framework to promote the security level of patient-related data.
- Blockchain ledger can be integrated with the framework as a model to store and extract the knowledge of CTs.

This paper has some limitations:

- The findings of the literature review are based on data collected from academic journals that spanned 5 years (2015–2020). Future research could be worthwhile to focus on practitioners' literature.
- The findings were based on the Medicines and Healthcare Products Regulatory Agency (MHRA) CTs route map. Further research could be worthwhile to adopt the developed framework based on other regulating agencies' roadmaps.

Conclusion

Pharma4.0 is a manifestation of Industry4.0 in the pharmaceutical industry and can be defined as employing the CPT in any stage of the medical development life cycle. It will not just help drug development and clinical research stay ahead, it will also be crucial to mission completion. This paper first presents an overview of work in the area of AI and ETD applications in clinical research and presents their shortcomings and limitations. The need for a system with real-time data acquisition, monitoring, and control capabilities is discussed in detail. A Pharma4.0 perspectival framework for clinical trials is presented and the role of the cloud-based computational unit and ETDs are highlighted. The proposed framework contains core entities including the sponsors, CBCU, CROs, and regulators/ethic committees. The third-party engagements are also considered as supportive entities. The developed framework offers three benefits, in that it (a) improve the smartness of the entities (i.e. human, tools, and devices), (b) connect and integrate smart enablers, and (c) providing real-time status and awareness information to the stakeholders and the regulating organizations.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1. Table 1. Illustration of some of the recent works in clinical research that use artificial intelligence, machine learning, and deep learning methods and tools to predict response following input data

Table 2. Some of the newly developed and employed embedded tools and devices with their domain of applications in clinical research

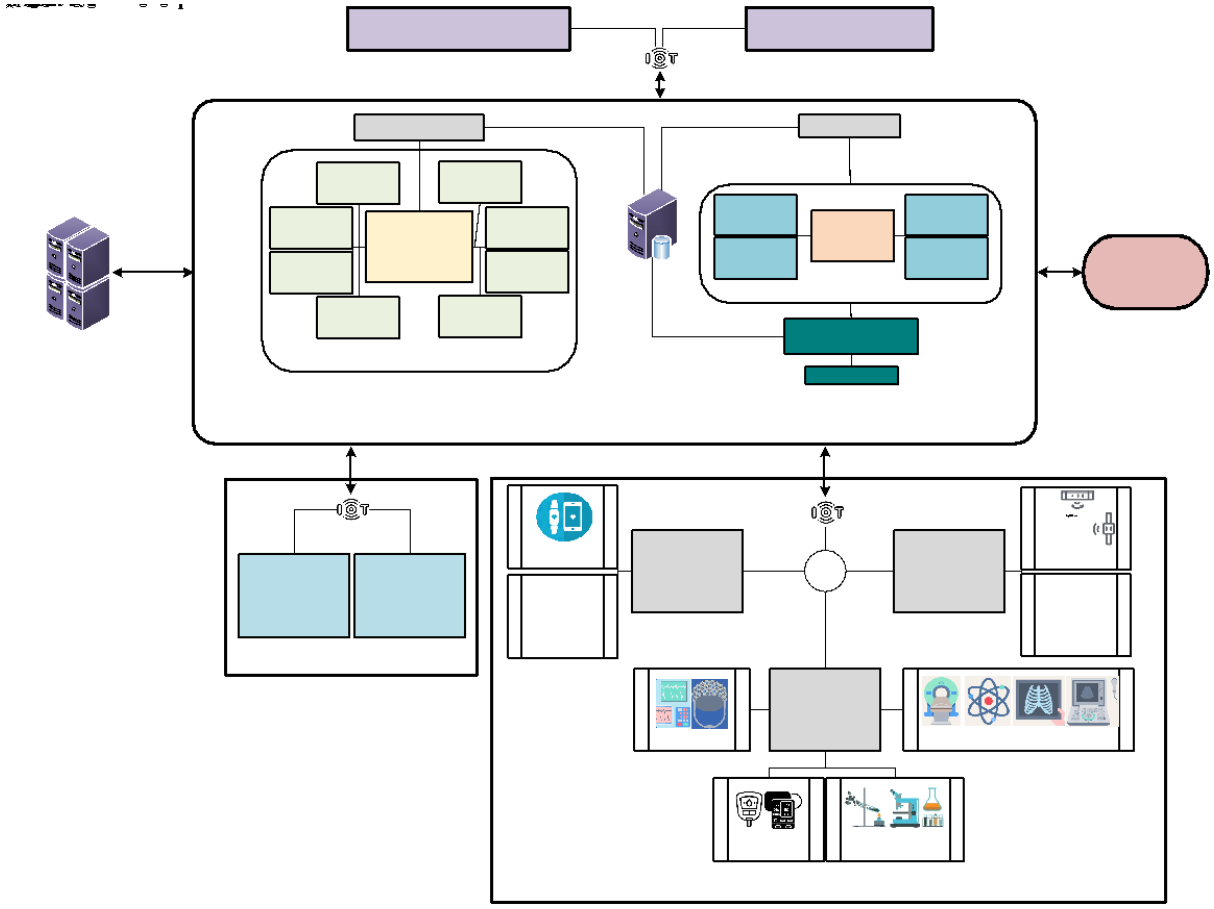

Figure 1. illustrates the core and supportive entities of the Pharma4.0 Clinical Trials Perspectival Framework. The sponsor(s), CROs, cloud-based computational unit, ethic committees, and regulating authorities are considered as core, and the clinical trials data providers, and third-party engagements are considered as supportive entities. Each of the entities provides/requests a service from the other entities along with the goal of the project. The entities are interconnected to each other using IoT and through the internet. CBCU is the heart of the system and it is deployed on a cloud. It provides planning, design, monitoring, and control services to the entities of the trial.

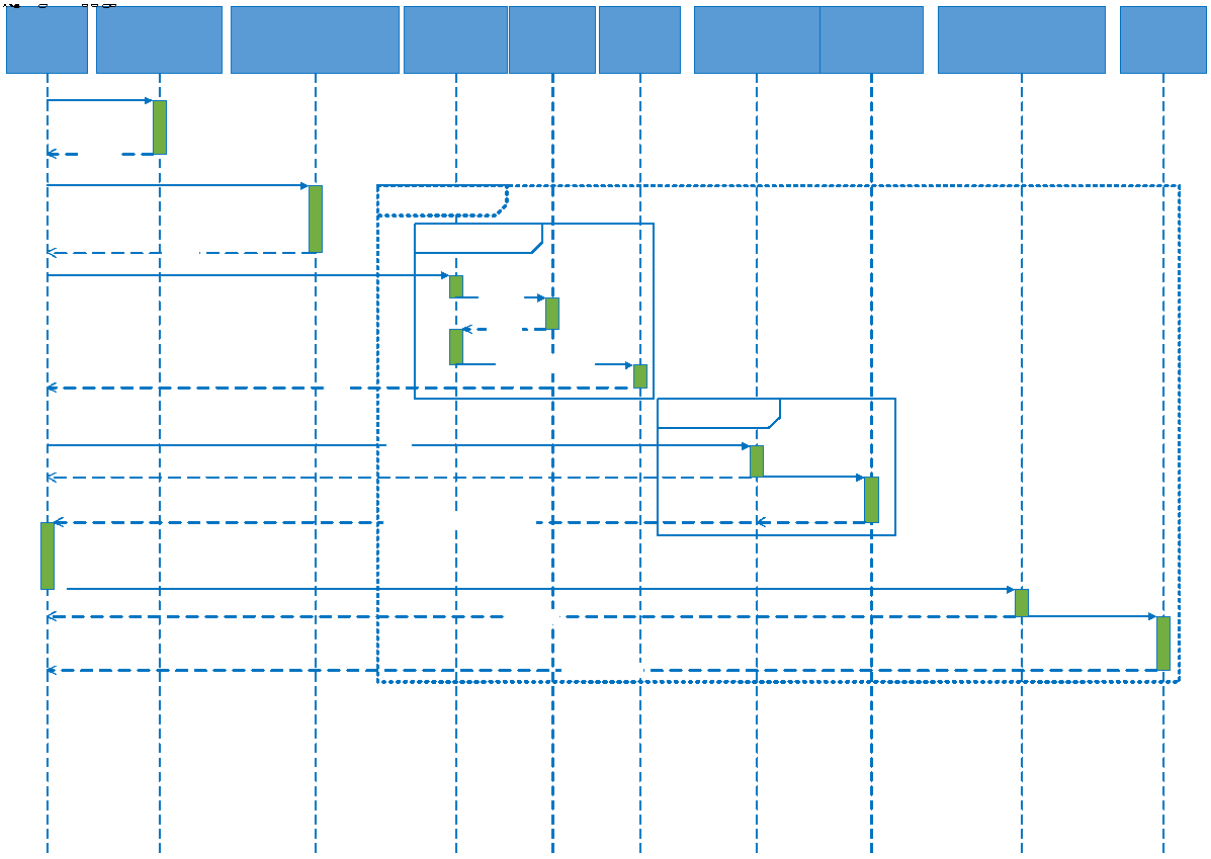

Figure 2a

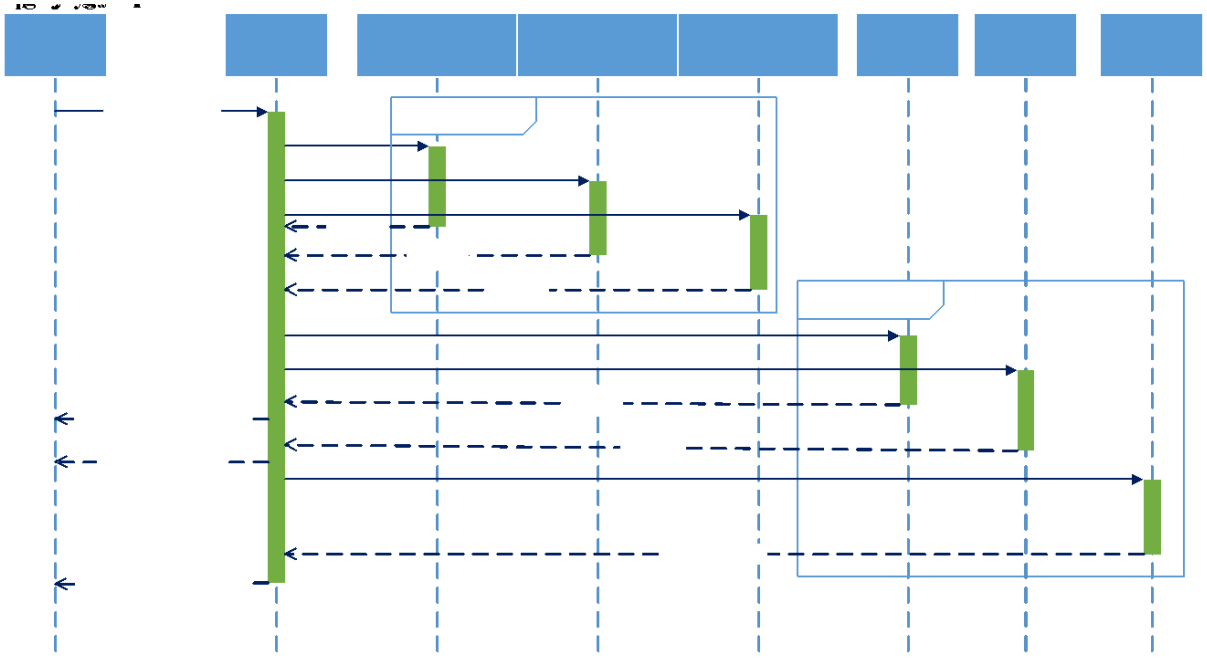

Figure 2b

Figure 2a. and Figure 2b represents the sequence of the processes and their fruits within the plan/design and monitor/control units of the CBCU entity. The actors provide a response following receive a query from the sponsor. For instance in plan/design, the sponsor asks the protocol

development team to prepare the protocol of the study which is forwarded to the QbD actor to prepare control strategies of the project based on the Plan, Do, Check, And act approach. The developed control strategies are used by the method design actor to prepare the dynamic plan of the project.

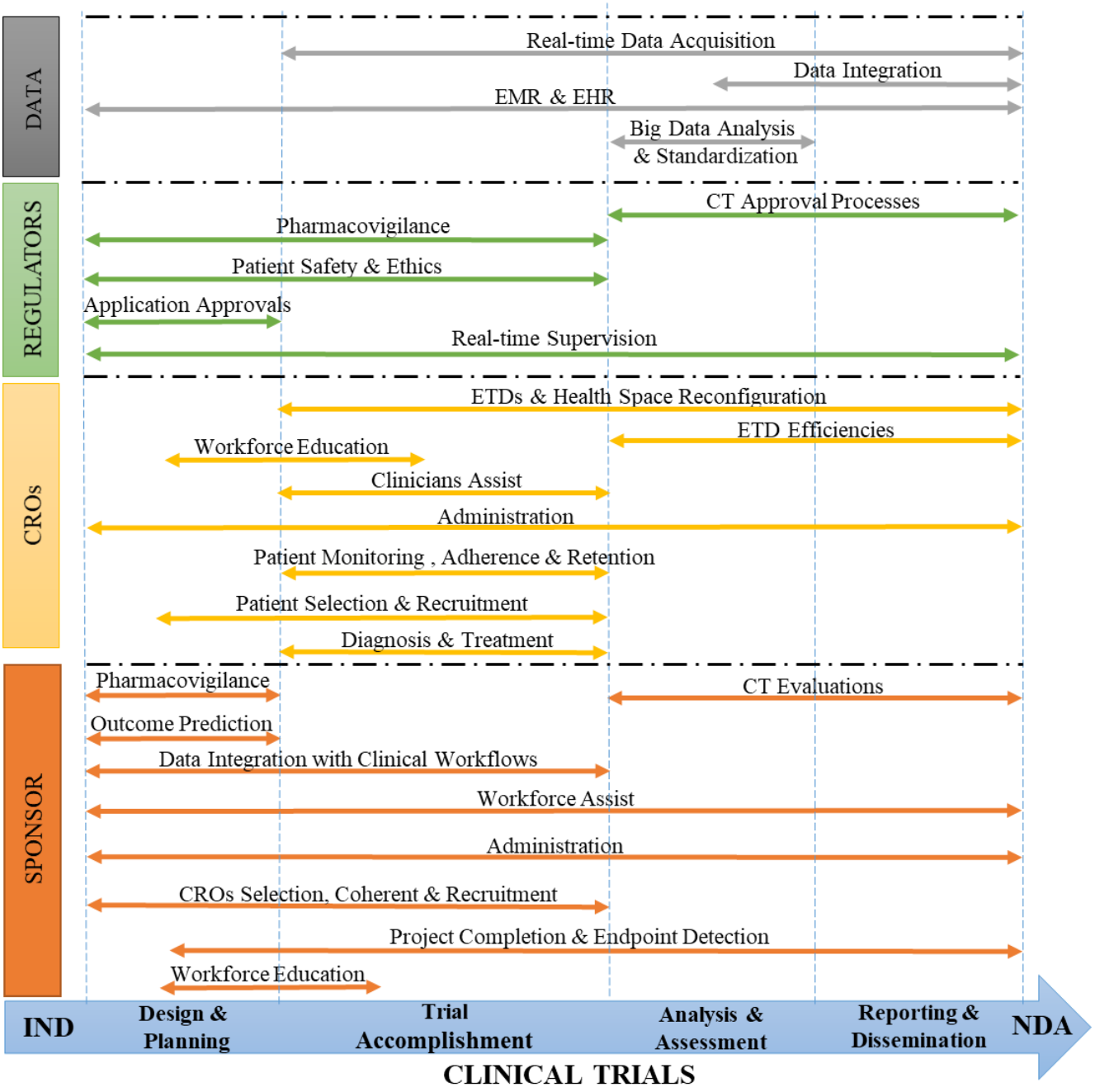

Figure 3. Possible impacts of Pharma 4.0 in the sponsor, CRO, and regulators as the key contributors of clinical trials and the data as the integrator along with the clinical trials life cycle. The clinical trials life cycle is categorized into four steps of design & planning, trial accomplishment, analysis & assessment, and reporting & dissemination. The lifelong impacts are represented with arrows.

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