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Research Protocol

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Abstract

Background: Advanced therapies, including cell and gene therapies, have shown therapeutic promise in curing life-threatening diseases such as leukaemia and lymphoma. However, they can be complicated and expensive to deliver due to their sensitivity to environment, troublesome tissue, cell, or genetic material sourcing and complicated regulatory requirements.

Aim and objectives:
This study aims to create a novel connected supply chain logistics and manufacturing management platform based on blockchain, with cell and gene therapy as a use case. Objectives are to define the requirements and perform feasibility evaluations on the use of blockchain for standardized manufacturing and establishment of chain of custody for the needle-to-needle delivery of autologous cell and gene therapies. A way of lowering overall regulatory compliance costs for running a network of facilities operating similar or parallel processes will be evaluated by lower monitoring costs through publishing zero-knowledge proofs and product release by exception.

Methods:
The study will use blockchain technologies to digitally connect and integrate supply chain with manufacturing to address the security, scheduling and communication issues between advanced therapy treatment centres and manufacturing facilities in order to realise a transparent, secure, automated and cost-effective solution to the delivery of these life-saving therapies. An agile software development methodology will be used to develop, implement, and evaluate the system. The system will adhere to EU and US Good Manufacturing Practices and regulatory requirements.

Discussion:
The successful implementation of the integrated blockchain solution to supply chain and manufacturing of advanced therapies can push the industry standards towards a safer and more secure therapy delivery process.

Keywords:
Blockchain, digital health, internet of things, regenerative medicine

Introduction

Advanced Therapy Medicinal Products (ATMPs) industries, including cell therapy and gene therapy, are forecasted to grow at a compound annual growth rate (CAGR) of 22% between 2018-2022 [1]. ATMPs are estimated to be a billion Eurodollar industry and potentially the fourth therapeutic pillar of healthcare [2,3]. Commercially available ATMPs make up a very small percentage of total patient interventions as compared to mainstream 1st and 2nd line therapies in the developed markets. However, for cell and gene therapy they are expected to grow from a few 1000 patients in 2018/19 globally to possibly 100m by 2025 as the number of ATMPs commercially available matures [1].

To facilitate the growth of the ATMP sector, the supply chain infrastructure is critical in supporting the industry from clinical trials to commercial distribution to provide life-saving treatments to more patients in a safer and more secure manner. In addition, compliance with data protection laws (Health Insurance Portability and Accountability Act [HIPAA] in the US and General Data Protection Regulation [GDPR] in EU) come with a very high cost [4–6]. Without proper encryption and selective data disclosure, everyone in the supply chain will have to be GDPR compliant. Key to the success of these new treatments will be the safe, secure and timely delivery of advanced therapies in a highly regulated environment (e.g. temperature, tilt, time duration, location) to ensure transparency and accuracy [7,8].

Current logistics tracking solutions are reliant on paper audit trails and legacy cloud infrastructure and are at significant risk to causing treatment failure. Specific to autologous therapies, the starting material collected from the patients can vary greatly. This can cause the final manufactured product to be of different quality and may fall out of specification[9]. For example, Novartis had to write off multiple batches of Kymriah (Novartis, Basel, Switzerland) due to out-of-specification products since its launch in August 2017 in the US[10]. Also, during the clinical studies, 7-9% of patients did not receive the CAR-T treatment due to manufacturing failures [11].

Current solutions, using paper and dated legacy standalone IT infrastructure that are being used by bioscience companies' pre-commercialisation maybe sufficient during research, but is likely to fail as their operations scale up and out. They are not designed to be scalable, interoperable or able to deal with the complexity of regulation and process that these ATMPs will incur as you enter the real world of patient care. Batch identification through patient initials and date of birth is considered insufficient due to possible mix-ups which can be catastrophic for patients. Intuitive labelling methods must be simple enough for use across sites whilst providing sufficient information about the patient to avoid mix-ups [12]. Companies, including Trakcel, Vineti, Danaher (previously GE), are using cloud-based solutions for manufacturing ATMPs [13–15]. Whilst cloud-based solutions systems are useful in tracking and tracing products in traditional linear logistic supply chains, data in these

centralised systems are highly vulnerable to being tampered with, potentially allowing fraudulent or damaged products entering the supply chain or data falsification. These systems focus only on the logistics part of the delivery process and fail to address the coordination issue between stakeholders (hospitals, patients, manufacturers, logistics providers, regulatory authorities) in advanced therapy delivery process.

As new licence indications are achieved, the systems will need to be designed to change and adapt across the whole logistics supply chain. From the collection of source material to the manufacturing and final delivery of therapies, there are many hand-off points and hence the probability of mix-ups and supply chain failure. As most advanced therapies are given as the last line of treatment for critically ill patients, the failure or delay may cost them their chance of survival.

Blockchain technology is a digital ledger of transactions, agreements and controls that are stored in a distributed network, removing the need for a centralised database. Due to its distributed and transparent nature, data stored cannot be tampered with and is transparent, traceable and secure [16,17]. The benefits of the technology have been explored in various sectors including finance, healthcare and agriculture[18–20] and one of the most highly discussed use case is in supply chain management. Integration of blockchain into supply chain architecture can lead to a more reliable, transparent and resilient system[21–24]. Specific to ATMP supply chain management, a layered blockchain solution with a smart contracts business logic layer can enable a holistic way of managing various stakeholders, ensure needle-to-needle supply chain integrity and secure data management. The decentralised nature of blockchain can allow this to happen almost instantaneously across the full ecosystem, including the ability to keep regulators updated by publishing on a public chain with zero-knowledge proofs. This is something that cloud environments cannot do and requires on-site regulation by regulators. The protocol of this study will focus on developing a patient-to-patient blockchain-based supply chain system for advanced therapies.

Methods

Description of the blockchain-based supply chain system

This study aims to create a smart and connected supply chain logistics and manufacturing management platform based on blockchain, with cell and gene therapy as a use case. The data collected from sensors can be better connected using an interactive platform to improve coordination between stakeholders. To ensure the security of this platform which contains sensitive information from patient data to manufacturing protocols, blockchain allows a transparent, incorruptible yet encrypted way of tracking and tracing the environmental conditions of advanced therapies from its origins to final administration. This is particularly important to advanced therapies due to the requirement of cold chain delivery and the sensitivity of live cell products to fluctuations in the environment. The platform technology will allow real-time and centralised monitoring of the needle-to-needle process without compromising patient data security through selective disclosure of information.

Publishing zero-knowledge proofs when all steps are completed according to standard protocol can allow regulatory authorities and manufacturers with multiple collection centres and manufacturing facilities to manage by exception instead of looking through all data points and paper batch records to find regulatory breaches, allowing a reduction in regulatory monitoring costs. This can help improve consistency in all steps of collection, manufacturing and delivery across centres and allow issues to be identified and the process to be improved through learning from data. The system will adhere to EU and US Good Manufacturing Practices and industry bodies for healthcare distribution requirements.

Development and evaluation

This study will involve the components outlined in Table 1. An agile framework will be used for the development and evaluation of the system [25].

Table 1 Components of agile development and evaluation

Nr	Components
1	Stakeholder analysis
2	Customise and implement track and trace software platform
3	Migration and integration of software to blockchain platform
4	Case study for evaluation of the system

1. Stakeholder analysis

A detailed stakeholder map shall be derived, including the manufacturer of therapies, healthcare professionals who engage with the therapy delivery pathway, payors of the treatment for visibility of the chain of custody of the ATMP, the advanced therapy treatment centre (ATTC), hospital IT system implementation partner, supply chain track-and-trace provider, logistics provider, manufacturing facilities (including contract manufacturers), and regulatory authorities. Focus group meetings will be held to understand the points where regulatory/monitoring costs arises; how a network of facilities are currently managed; the data that needs to be collected at different points of the supply chain to enable cheaper monitoring and product release by exception. Outcomes will be user requirement specification for decentralised manufacturing, standardized workflow for target therapy, understand the capability and gaps in and across current systems.

2. Customise track and trace software platform

The design of minimum viable eco-system and definition of scope of work for each party will be produced. A working prototype track and trace software platform for autologous advanced therapies has been developed and will be customised to cell and gene therapy. For regulatory activities, we will extend existing regulatory approval to complete preliminary pathways for support of our new product. The platform will be designed so that it can be easily integrated into existing commercial applications or be a standalone solution if required. A customised prototype will be developed to demonstrate the platform.

3. Migration and integration of software to blockchain platform

The prototype track and trace software platform will be adapted to combine characteristics of linear and circular supply chain for advanced therapies. Key outcomes to monitor will be communication time reduction; capacity utilization; resource sharing and utilization; ease of establishing process comparability across manufacturing facilities; delivery accuracy and number of mix-ups/failures; user satisfaction (ease of use, interoperability, etc).

The core code of blockchain technology platform for solutions currently developed are patented in the US and EU [26]. Compared to existing local electronic batch record system and cloud-based solutions, a blockchain-based platform will allow for a more secure way of recording and storing supply chain data on a distributed ledger and encrypted to make blockchain technology tamper proof. Any divergence or discrepancy to the ledger of information captured will be flagged to all, including the authorities.

Participating parties can manage the system so that only the relevant information is made available to each party. A blockchain solution facilitates partnerships between parties with divergent commercial self-interests leveraging automated smart contracts. Each party is kept honest as the collective objectives of all consortium members using the blockchain solution will not be beneficial to any of the members if members were to collude. Real-time and up-to-date manufacturing process updates to be transparent for patients and hospital

staff in order to allow more efficient scheduling and resource allocation for treatment preparation. This means that the hospital can provide patient status updates to manufacturing. Information on the blockchain can be encrypted and selectively available to approved parties, hence reducing the number of European General Data Protection Regulation (GDPR) trained staff, thus lowering the cost of compliance.

Through integrating the track-and-trace and manufacturing execution system, greater coordination between stakeholders can be fostered, allowing the delivery process to be more efficient and releasing valuable time of skilled workers for value-added work. Good track and trace documentation will allow manufacturers and hospitals to go back and look at what may have happened differently to better understand what can improve the outcomes and hence improve the quality and consistency of raw material collection and manufacturing process.

Use of blockchain will ensure data integrity between the various systems, scanners and data input devices without having to make substantial integration changes. Also, this creates efficiencies through automating payment processes, regulatory reporting, compliance and audit. Also, this technology can lower the cost of regulatory compliance through publishing zero-knowledge proofs where all standard protocols are done properly, removing the need for going through all records (on paper or in cloud) and the cost of GDPR compliance training through encryption of patient data and implementation of multiple levels of access rights.

4. Case study

This investigation will be structured via a six-stage process for case study investigations [27]to evaluate the system's feasibility and economic impact. A case study will provide a structured means to generate evidence to subsequently evaluate such claims by collecting baseline data for further evaluation. Understanding the feasibility and economic impacts of blockchain for cell therapy in a decentralized fashion at different levels of automation, different demand levels and scale of system. Project outcomes appraisal and simulate the impacts of widespread use of this methodology for larger systems through modelling. The results will be disseminated through publications and conference presentations.

Table 1. Case study framework

Stage	**Outcome**
Plan	Case description and linking of case approach to investigation outcomes.
Design	Construction of research design and linkage of research questions, data, and criteria for evaluation and synthesis.
Prepare	Draft, execution, and approval of study protocols.
Collect	Data collection strategy.
Analyze	Data extracted into categories for review and analyzed.
Share	The findings will be presented in a report for publication in a peer-reviewed journal.

Discussion

The successful implementation of the integrated blockchain solution to supply chain and manufacturing of advanced therapies can push the industry standards towards a safer and more secure therapy delivery process and encourage rapid adoption of the innovative technology. Adoption of the innovation in a wider context can reduce the cost of monitoring good manufacturing practices through increased transparency and security of the manufacturing and delivery process. A more transparent process can reduce communication errors and overall time spent, hence reducing healthcare costs. The integrated platform solution will enable more accurate and transparent tracking at all stages of the needle-to-needle delivery pipeline, allowing treatment centric care pathways to be truly personalized through a digital evolution in supply chain and manufacturing management.

Authors' contributions

Ching Lam, Michelle van Velthoven, and Edward Meinert wrote different parts of the protocol.

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Competing interests' statement

None stated.

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