International

# CLINICAL TRIALS

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Small sponsor companies are being encouraged to collaborate with CROs to better delivery

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# Clinical Connectivity

**Using modern digital technologies, today's research networks are embracing new ways of more intimate collaboration and constructive improvisation to increase the speed and quality of clinical research**

Andreas Walter and Le Vin Chin at Clinerion

A clinical research network is a gathering of like-minded research centres, usually academic institutions or teaching hospitals, coming together to pool expertise, best practices, tools and equipment, and resources and manpower, with the goal of furthering their research capabilities in ways that no single institution could achieve alone. In the main, these are self-assembled and self-organised regional clusters of hospitals.

Banding together, clinical research networks benefit from sharing best-in-class clinical expertise, facilities, and equipment. Not every hospital's research department is funded well enough to be able to afford a SPINlab Hyperpolariser, or an in-bore MRI targeted ultrasound device, which can run into the millions of pounds. Similarly, other tools, such as software solutions, need only be purchased once to benefit the entire network. Depending on the set-up of the network consortium, the set-up and management processes of a clinical trial may also be simplified, such as only one ethics committee approval being needed for the entire trial, across multiple sites.

More importantly, having access to patients from every member institution, the network gains a larger pool of potential patients for its research. A heterogenous grouping of research facilities also allows the research network to have expert personnel in a variety of fields and facilities suiting many treatment methodologies.

All this means an increase in opportunities for clinical researchers to participate in leading-edge clinical research and more opportunities for patients to gain earlier access to new and better treatments through participation in research.

## The Evolution of Digital Adoption

Clinical research networks have been around for as long as more than one research hospital has existed. However, a new ongoing trend towards digitalisation of hospital data is also enabling the network to perform its research much more effectively: interrogation and analysis of records and results become instantaneous and exhaustive.

The Healthcare Information and Management Systems Society Analytics defines the parameters for the level and quality of digitisation of hospitals with its Electronic Medical Record Adoption Model (EMRAM), cataloguing hospitals' achievements. As of 2017, 5,480 hospitals in the US and 1,462 hospitals (as of 1 January 2017) in Europe have had themselves evaluated, and statistics show that hospitals are moving into higher EMRAM stages – ie, high levels of digitalisation – as time goes by (1-2).

Digitalisation of hospital data supports the recording, storage, and analysis of patient health data, allowing huge efficiency gains, transparency of the number of patients, hospitals and treatments, and the mapping of data from trials, making them comparable. A 2013 paper analysed the correlation between the degree of digitisation of a hospital and a patient's experience of care, and the results found that hospitals with exceptional levels of digitisation (EMRAM Stage 7) showed significantly higher care scores (3).

The importance of healthcare digitalisation is why the FDA has released three new draft guidance documents to clarify its position on digital health, as part of the 21st Century Cures Act (4-6). As summarised by *Applied Clinical Trials*, "the release of the guidances can facilitate digital health device validation for disease-specific indications, which can then be used to objectively measure outcomes in clinical trial endpoints" (7).

## How Digital Technologies Help Clinical Research

The digitalisation of healthcare is allowing healthcare data to be used much more effectively and efficiently for clinical research. This covers the entire process of drug development and launch, from clustering disease incidence, to identifying patient clusters for testing, to gathering real-world evidence, and tracking patient outcomes. Having electronic health records (EHRs) for patients means their data can be queried and analysed in real-time, providing more sensitive and comprehensive information for the quick and early detection of indications and patients. EHRs also offer a direct link to the physician and not just the patient.

A researcher can easily send queries based on complex criteria and find numbers of patients at a hospital who fit those criteria. Using Big Data analytics techniques to gather, make sense of, put into context, and draw useful conclusions from large swathes of EHRs can generate useful data for real-world evidence, as well as disease epidemiology and pathways within a hospital's population.

With the same query, a clinical trial manager at a hospital can (with ethics committee approval) identify patients eligible for their trial. This approach would also work in the search for patients for personalised medicine (8).

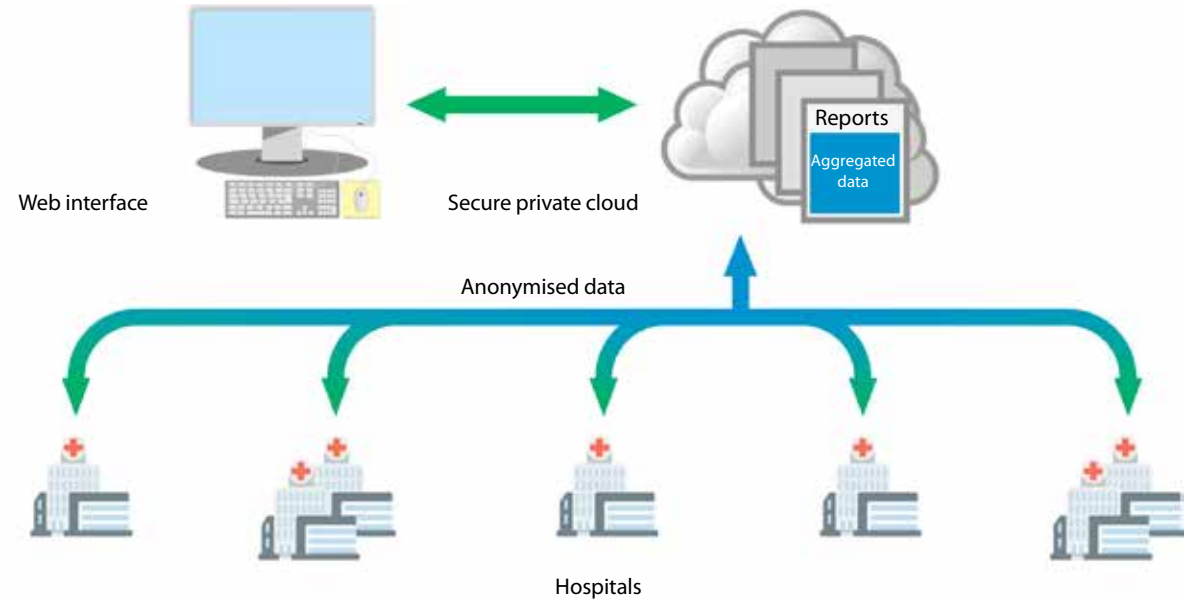


Figure 1: A hybrid platform of federated local installations and a secure private cloud

Digital technology is already in use in the electronic data capture of patient details (treatment programme, dosages, lab results, etc) during a clinical trial. Having data available in electronic form also allows the transfer of prior health data from the hospital's information system to the clinical trial's patient data database to complete the patient's electronic case report form without complex and expensive processes of manual data entry and source data verification.

The industry is developing an entire ecosystem of digital health and mobile health technologies dedicated to capturing health data points from across daily lives. These help to fill in the gaps when building a picture of an individual's health, support treatment, or compliance monitoring and, ultimately, efficacy. They also enable remote trials (ie, trials which are not bound to particular research sites). In 2017, Novartis announced a US $100 million investment in digital technologies, both 'around the pill' and 'beyond the pill' explaining: "around the pill applications are technologies that support or enable the efficacy of our drugs… Beyond the pill technologies might include digital therapeutics" (9).

## Associated Issues

EHR-based search and identification of patients is now an accepted methodology in institutions, with the benefit of providing rigorous search independent of individual fallibility. What happens when a research network or consortium brings together multiple institutions?

**Accessibility**
EHR systems often do not have tools to search on large scale, even within the various departments of an institution, as the patient data is often siloed. Continued complexity arises when considering the set-up of a research network, wherein the parties will want to access a wider group of patients' data, with tools to search on a large scale across multiple institutions in the entire network.

**Data Harmonisation**
Patient data standards (terminologies and codes for key descriptors, such as disease diagnoses, treatments, demographic information, laboratory results, and medication prescribed) will also differ between institutions, making a search across systems additionally difficult. The system will need to query multiple hospitals at once in their own 'language'.

**Patient Privacy and Data Security**
Issues also surround patient privacy and the security of the data. Within a consortium, the parties will generally want to allow a certain level of data sharing and querying of patient data, while still respecting the individual hospital's responsibilities regarding patient data.

Patient privacy has gained greater prominence with the EU's General Data Protection Regulation (GDPR), which came into full force in May 2018 and codifies the rights and responsibilities of the gathering, storage, and use of patients' personal medical information (10). Whether within the EU or not, all techniques for gathering, storing, managing, and using the data are expected to be legal according to local laws.

The use of EHRs also raises questions about how secure the data is and where it resides from attack, being accessed by unauthorised players, or being hacked.

**Scalability/Modularity**
A research network requires modularity in its infrastructure, so that members may be added or removed without needing to rebuild the platform from scratch. Each hospital will have a different hospital information system (HIS), and it must be possible to add new ones to the query process in a consistent, modular way with minimal effort. Members must also still have 'control' over their own data and the choice to participate on a per project basis with the capability to share data selectively.

**Real-Time**
Assuming each hospital maintains its patient data up-to-date, allowing the entire network's system to reflect the data in real-time is an issue.

Most of these concerns speak against the traditional solution of pooling data to a central 'warehouse'. A model in which queries might interrogate data from multiple sites while maintaining scalability, data security, and access to real-time data would be needed. Options of installing a centralised cloud archive were analysed (wherein regular updates of patient data would be drawn from connected hospitals to a centralised cloud environment) and a peer-to-peer network (wherein each peer may query data from other peers), both of which were discarded, concluding that neither could meet the challenges set above (11). A centralised cloud archive would not be able to work in real-time, nor would patient privacy be satisfied if data were to leave the hospital environment. A peer-to-peer network would require creating network entry points to each node, which hospital IT administrators are usually unwilling to do because of the risk of hacking.

## Possible Solutions

One solution is a hybrid platform of federated local installations and a secure private cloud (see Figure 1, page 23).

The local installations are nodes at each hospital which are loaded with just that hospital's (anonymised) patient data and are under the full control of the local hospital IT administrator, who may choose to decide in every case whether to accept an incoming query request. The queries themselves are held on the secure private cloud, which distributes the queries to the federated nodes at the hospitals. The resulting count of patients who fit the criteria is returned by the node to the cloud for aggregation.

**Accessibility**
Such a system would allow searches to extend across locations, whether departments within a single site, across sites, or across institutions in the research network. Each location is simply a node in the system which communicates independently with the cloud. All nodes would be able to take advantage of the full search functionality of the system, operable from the web, making it easier than requiring IT assistance on each occasion at each node.

**Data Harmonisation**
By applying semantic technologies to render the queries and the returned results semantically interoperable at each node, differing data standards may be accommodated. This offers the flexibility of being able to integrate with different HIS and data formats, offering a standardised method of data access independent of what EHR system each hospital is using and thereby allowing simultaneous searches across all hospitals in a network, regardless of their differing HIS systems and dictionaries.

**Patient Privacy**
The clear solution to this challenge is to ensure the data is never removed from the hospital at any point. With the cloud/federated node set-up, no identifiable patient data leaves each hospital's secure environment. Only anonymised patient data is loaded onto the local node, and access to that is still governed by the hospital's own IT policies and processes. The cloud itself contains no individual patient data, just aggregated results and metadata.

**Data Security**
Each hospital remains in control of query channels, and its connection with the cloud is at its discretion. Therefore, no open inbound connection exists from the cloud to the local server nodes at the hospitals. This means the cloud cannot initiate a connection with the nodes, and, therefore, they cannot be hacked from the cloud.

**Scalability/Modularity**
As each node relates to one department or site, adding a new research consortium member simply means adding another node, making the overall system linearly scalable and simplifying expansion. As these nodes may even be virtual servers in the hospital's IT infrastructure, speed of implementation may be quick, the requirement for human resources for application may be low, and, therefore, costs may be minimal.

**Real Time**
While daily updates from the HIS to the local node are usually sufficient, immediate updates can be activated by demand, making the results of each query effectively real-time.

**Protocol Optimisation**
As queries may be sent at any time to query the live network, protocols may be optimised as they are being developed. The protocol may be coded as a query and then tested on the full population of patients within all the hospitals of the research network's databases.

## Anonymised Identification

According to the EU Data Protection Directive, as well as the GDPR, secondary uses of person-specific data without individual consent are strictly prohibited, with the exception of "data rendered anonymous in such a way that the data subject is no longer identifiable" and "personal data rendered anonymous in such a manner that the data subject is not or no longer identifiable" (10, 12). This can be seen as a general principle for most regional regulations.

Therefore, an optimal solution for the reuse of patient data for clinical research purposes is to use exclusively anonymised data. This enables the analysis of real patient data for real-world evidence data generation, optimisation of protocol design, and trial site selection, using all available information.

In comparison with the use of pseudonymised patient data – the standard until now for EHR networks – the use of anonymised patient data did not allow search and identification of individual patient candidates for trials. The use of pseudonymised data was a real efficiency boost and time-saving factor for clinical trials, but is becoming problematic as GDPR places heavy regulatory and compliance burden on the use of pseudonymised data, effectively de-recognising the privacy protection offered by this technology: "Personal data which have undergone pseudonymisation, which could be attributed to a natural person by the use of additional information should be considered to be information on an identifiable natural person." (10).

A new technology can provide a solution called 'anonymised identification', which allows re-identification of previously anonymised candidate patients by authorised trial staff members at respective hospitals (13). The method functions by a combination of techniques to match anonymised records with corresponding hospital medical records in the original hospital's HIS. In this way, no identifiable patient data is ever exposed to a third-party, and the patient may still be found and screened for enrolment in a trial, ensuring patient privacy.

## Cloud Clarity

Use of the distributed network helps narrow the search space for finding potentially eligible patients, while ensuring the challenges of accessibility, data harmonisation, patient privacy, data security, scalability, and real-time use are all met. The cloud approach is disruptive to the industry and creates a new paradigm, as it offers transparency on how many potentially eligible patients can be identified at each participating site in a network, giving pharmaceutical companies or CROs a metric to select sites and then to 'measure' their recruitment performance.

With the next developments, it will be interesting to see whether blockchain technology will support the cloud-based approach and reduce anxiety about privacy. A way is yet to go to reach the target endpoint, wherein all suitable candidates will be found via electronic means only, but these steps are firmly heading on the road of improved efficiency.


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