Data in Motion: Advancing Real-Time Exchange, Interoperability, and Standardization in Clinical Trials

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Introduction

As the landscape of clinical trials evolves towards more decentralized approaches, we're seeing an explosion in the variety of data sources. The need to move and manipulate data is growing just as fast. From electronic consent forms (eConsent) to patient-reported outcomes (ePROs), and wearable technologies to direct patient services, the ways in which we collect and analyze data are expanding rapidly. This shift is not just about collecting data through new channels like electronic health records (EHR) and patient registries for Real World Data (RWD), but also about how this data can drive Real World Evidence (RWE) to power the next generation of medical breakthroughs.

In this rapidly changing environment, the principles of Good Clinical Practice (GCP) guide us to ensure that our methods appropriate, high-quality, and tailored to meet the unique needs of each study. However, the complexity of managing quantities of data and data integrity grows as trials become more decentralized, highlighting the need for increased efficiency and advanced data governance that moves beyond traditional methods.

This paper introduces a vision for a new, digitally-driven approach to managing clinical trial data. We propose a framework based on industry-wide cooperation around metadata and event-driven processes. This framework would enable:

1. The centralized registration of clinical trial systems and their metadata, facilitating seamless data integration across various platforms.
2. The use of events to automatically trigger the secure exchange of data between systems enabling increased efficiencies, improved data accuracy, and real-time synchronization of data.

Our approach takes cue from innovative practices across various industries with a focus on real-time data and event-driven processes that enhance user experiences and operational efficiency.

Consider the sophisticated notification system employed by Uber. When a user requests a ride, Uber's system not only matches them with a nearby driver but also keeps the user informed at every step of the journey…from driver acceptance to arrival at the user's location. This seamless communication is powered by a complex event-driven architecture, where each event (ie, a driver accepting the ride request) triggers a notification to the relevant user. This example highlights the power of leveraging metadata and event-driven processes to streamline interactions and processes. Just as Uber intelligently connects riders with drivers and provides timely updates, our proposed framework aims to connect clinical trial data sources and systems, ensuring that critical data flows efficiently and securely across the clinical trial ecosystem.

The aim is to bring these proven principles into the realm of decentralized clinical trials, advocating for a framework that prioritizes simplicity, adherence to best practices, and the avoidance of unnecessary new standards. This initiative, which seeks to chart a course towards more connected, efficient and effective clinical trials, was first introduced at the DTRA Annual Meeting in November 2023 by the following industry leading consortium of partners:

- EDETEK
- Merative

- Realtime-CTMS
- Frank Healthcare Advisors

Embracing this vision, we are confident that the clinical trial industry will achieve unprecedented levels of integration and automation in its data processes. This will lead to faster and more reliable outcomes for trials of the future. While these concepts will have a profound impact on decentralized clinical trials, they also have far-reaching impacts on the clinical trials industry as a whole since data transmission efficiencies and quality improvements are needed across all trial types.

Secure Registration of Systems and Source Metadata

Modern IT operating systems implement programs that allow for automated registration of applications and supporting pathways for configuration and data. As users of Windows, iOS, and Android devices, we are intuitively familiar with "Add/Remove" features that can quickly install and delete applications and their data. These registration records are also leveraged in support of connected upgrades, maintenance, and backup/restore of data and configuration files.

Within the context of a clinical trial featuring decentralized elements, sponsors and CRO's will quickly contract and group any number of bespoke vendors offering "fit for purpose" applications and platforms. These vendors and systems contribute additional data sources and clinical evidence in support of clinical research, yet unlike the devices we hold in our hands, there is no single, central point of registration for decentralized systems and data.

A central point of electronic registration for clinical trial systems and source metadata is needed to provide a foundation for system endpoints and data discovery.

System and Metadata Discovery

The proliferation and ubiquity of RESTful API's in support of interoperability and real-time messaging offers a means to enable a secure central point of registration for all IT systems that participate in a clinical trial. The n:1 ("many-to-one") relationship between participating systems and a central study metadata registry actor can be enabled by development, promotion, and decentralized clinical trial (DCT) technology vendor adoption of the following best practice:

Every clinical trial technology vendor SHOULD implement an API endpoint according to an intuitive, standard URI convention that returns the following data to an authenticated and authorized requester:

- Vendor name and company URL
- Vendor product name and information
    - Product software version
    - Classification (eConsent, ePRO, eCOA, wearable technology, etc)
- Hosting information
    - Country/region edge implementation information

- Data dictionary
    - Listing of metadata: Objects, element names, descriptions, mappings (CDASH alias and other ontologies), PII flags, and URI endpoints used to access these constructs
- Supported events and activities
    - If the connected system participates in an event driven framework, a list of published event types can be provided here to support cross clinical trial system discovery of and subscription to these events

It is important to note that there needs to be industry agreement and alignment on a query and response structure to "describe" participating vendor systems and metadata. This will allow for consumption of the responses by a central "Study Metadata Registry" actor that records the API URL's and calls them to build an aggregated structure and view.

Study Metadata Registry

If the API endpoint standard described above is adopted and implemented by n vendors, then a central point of registration becomes feasible for decentralized clinical trial vendor systems and metadata. Upon implementation, this may be as lightweight and simple as a secure API endpoint that executes concurrent requests to the registered system endpoints to retrieve an aggregate of systems and metadata. A web or mobile application can consume or process this information. The Study Metadata Registry actor can also be queried in support of scripted automations within an event driven framework to automate data access, retrieval, processing, and integration between systems.

In addition to serving as an aggregation point for n system information and metadata registration, the centralized Study Metadata Registry can also securely host and share secure clinical trial and study identifiers that will need to be consumed by DCT systems. Some examples of these data elements may include:

- Sponsor name
- Study name
- Phase
- Disease/Condition
- Protocol
- Site numbers
- Countries

…and other study protocol metadata elements that are important to align across connected participating vendors in support of uniform data integrity. The n DCT systems that expose and share information with the Study Metadata Registry can also query for standard study metadata values to seed their local databases. *Upon aggregation of these disparate systems for statistical analysis, the value of automating integration of key study identifiers into disparate systems will be clear to CRO and sponsor clinical data managers.*

Below is an illustration of a prospective exchange of metadata between DCT platforms and a central study metadata registry. The transactions and data payload structures are offered to stimulate model design thinking.

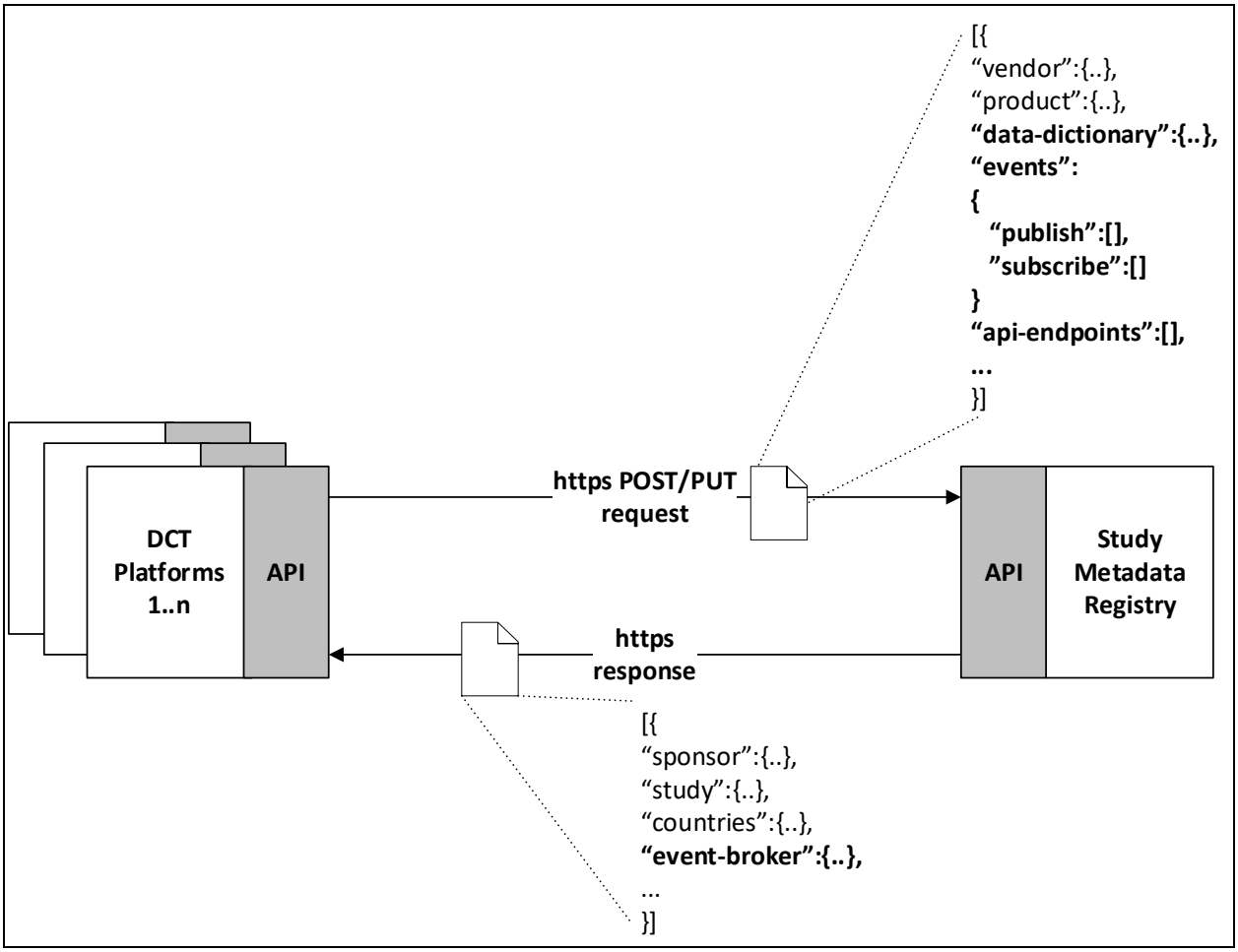

Figure 1: Registration of Clinical Trial Platforms

Event Driven Frameworks

Event driven frameworks are very common in industries outside of life sciences. These platforms support cross stakeholder subscription to and notification of published “events” of interest that occur in other systems. Once these event notifications are received by a subscriber, data can be streamed and processed from the source system that created and published the event.

Within a decentralized clinical trial, an eConsent platform may communicate the event of “patient consent completed” on signature/countersignature of document. Subscribing systems that wish to be notified of this event may receive a notification containing information about the event, or a reference to information about the event, that can be used to support automation.

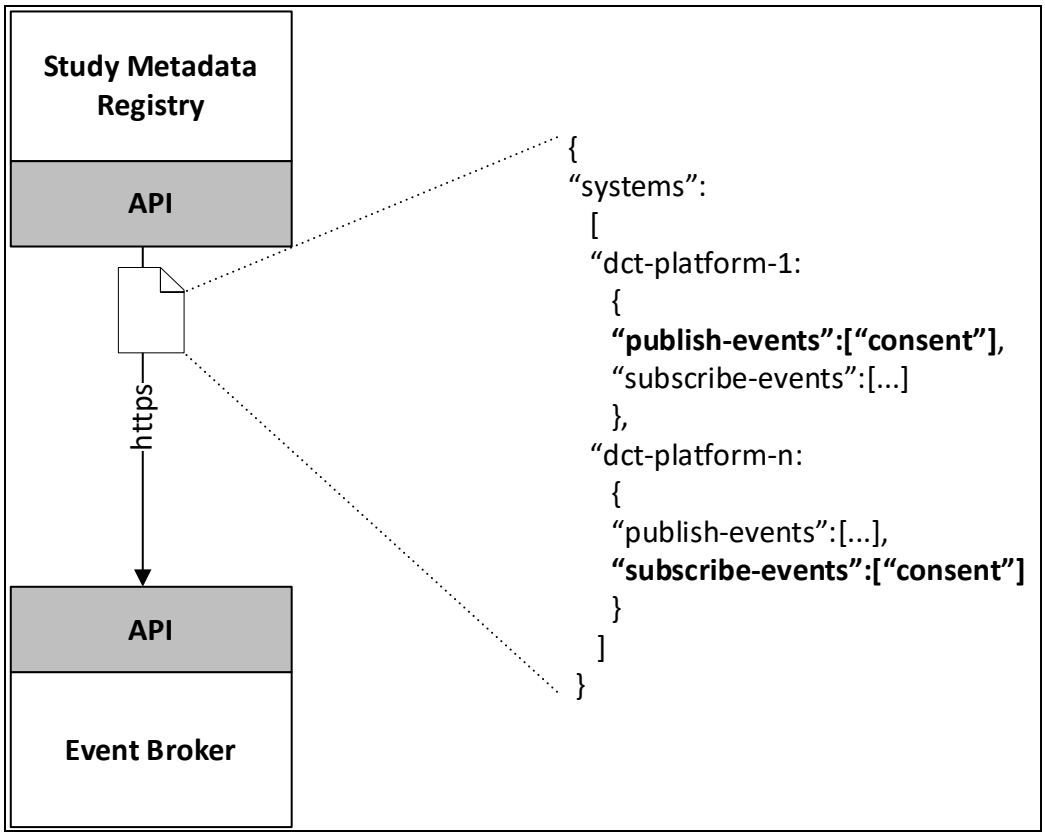

Figure 2: Configuration of Event Broker by Study Metadata Registry

Use Case Example

Consider the following narrative:

In support of a clinical trial, a sponsor or CRO has identified, vetted, onboarded, audited, and contracted with a collection of DCT technology vendors that are determined to be “fit for purpose” to the study requirements. As part of implementation and according to project phase, each DCT technology vendor provides the DCT project team with a secure URL that is used to register the DCT technology system with the central Study Metadata Registry. The Study Metadata Registry connects to each DCT system API endpoint and queries the endpoint for metadata describing the system, data, and events of interest to the system. The combination of the following:

- Metadata describing data objects offered by each system for study access
- Registered events of interest for each connected system

…provides the relationships between systems and data that will be processed for the study. This pairing of data availability and system(s) subscribing to the data objects can be used to inform the data processing and usage terms in an informed consent document. The relationships between requesting data subscribing and data object is also central to administering authorization and access to data.

In turn, each connected DCT system is provided with the URL endpoint for the Study Metadata Registry that allows for the systems to query and retrieve study and protocol identifiers and metadata that will normalize data common data values across connected systems. As the datasets generated by these systems are exported and aggregated for statistical and analytical processing, the maintainability of referential integrity will be higher if each data set was seeded with common values.

Patients that meet study inclusion criteria and screen successfully into the study are presented with consent language through an eConsent application and platform. As indicated above, the consent language may contain or reference relationships between data objects and connected systems that intend to process the data.

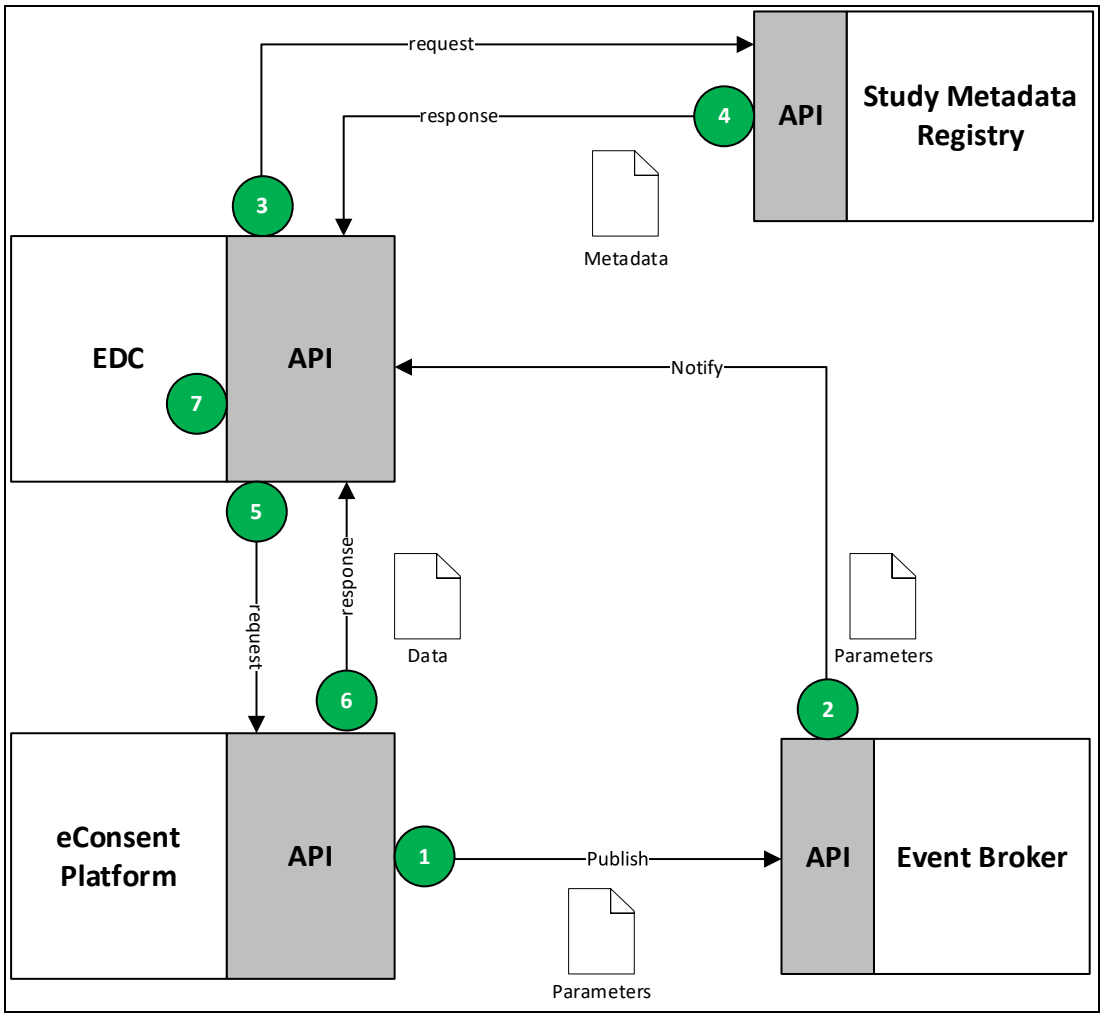

Figure 3: Sample Event Flow

1	Upon patient review and acknowledgement of the consent content, the eConsent application is used to execute 21 CFR Part 11 compliant electronic patient and investigator signatures. The investigator countersignature triggers publication of a "consent event" containing the IRT assigned identifier for the patient, as well as consent document object identifiers and descriptors in the eConsent system. The consent event is sent to the Event Broker, and includes the following parameters: • Subject identifier of the patient that consented • Domain name of the system that generated the consent event
2	The Event Broker receives the consent event and performs a lookup of the connected DCT systems that subscribe to "consent". In this example, the EDC is a subscribing system. The Event Broker notifies the EDC of the consent event occurrence and provides parameters that were included in the event.
3	Using the event and system name information provided in the parameters as a key, the EDC: • Creates a folder or storage area in anticipation of receiving and storing data for the consented patient • Queries the Study Metadata Registry to learn more about the system, endpoints supporting the patient consent event, and metadata of the eConsent platform.
4	The Study Metadata Registry returns metadata about the eConsent Platform. This information includes: • Base URL/IP address of the eConsent API • URI offset that serves up data corresponding to the "patient consent" event • HTTP methods (GET, PUT, POST) supported by the URI • List of data objects and elements provided by the patient consent URI endpoint • PII flags and mappings to CDASH aliases
5	The eConsent Platform uses the metadata returned in step 4 above to establish a connection to the API endpoint that supports the patient consent event. A request is issued against that endpoint that is constrained using the patient identifier received as a parameter in the notification received from the Event Broker.
6	A data object corresponding to the specific patient's consent event is returned to the EDC. The data might include: • Unique identifier for the eConsent system document object • Description of the consent document (ie, "ICF", "Technology Consent") • Date and time stamp for the patient signature and investigator countersignatures • URL link to a PDF version of the patient's consent document in the consent system
7	Supported by study context and system metadata, the EDC consumes the patient consent data object returned and uses metadata to route the data to the appropriate form, table, or object.

Security

As consumers of digital services, we are familiar with what has now become a common prompt in eCommerce applications:

"Third party application or service XYZ wants to access your profile information. Do you agree to authorize this access?"

This is an example of a very common and popular security authorization methodology called OAuth, which defines the role of a "Resource Owner" to authorize third party access to information.

Within DCT ecosystems, not only human interactions but also automated processes require access to sensitive data. OAuth addresses this need through a model supporting "machine-to-machine" (M2M) authorization. This variant of OAuth allows for secure, automated data exchanges between different systems and platforms without human intervention. It's pivotal for enabling real-time data processing and integration, ensuring that each system can perform its designated tasks efficiently while upholding stringent security standards. This mechanism ensures that each application accesses only the data necessary for its function, enhancing privacy and security.

Summary

As we stand on the cusp of a new era in clinical research, it's evident that the future of clinical trials is deeply entwined with technological advancement. The shift towards decentralized models necessitates a departure from isolated data silos to a more interconnected, responsive, and flexible data ecosystem. This evolution is underpinned by secure APIs, microservices, and a robust framework that facilitates seamless metadata registration, event-driven communication, and efficient data exchange among DCT platforms.

Industry Alignment

The principles and practices outlined in this paper are not novel inventions; they are tried and tested methodologies adapted from other sectors. Their application in life sciences and clinical research is both a logical step and a strategic necessity. By embracing these digital frameworks, the clinical trial industry can significantly enhance data integrity, streamline operations, and ultimately, accelerate the delivery of therapeutic innovations to patients.

Looking Forward

The rapid advancement of AI and machine learning technologies underscores the urgency of adopting these frameworks. As these technologies become increasingly integral to clinical research, the ability to swiftly and securely exchange data will transition from a competitive advantage to a fundamental requirement. The journey ahead calls for collective action, shared standards, and a commitment to innovation—a path toward transforming the landscape of clinical trials for the better.

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