Participant Digital Health Twin for Clinical Trials

ISMT E-599 Capstone Seminar in Digital Enterprise - Spring 2019

Team 3

Jon Polaski

Tamara Rogers

Jon Rydarowski

Marty Stogsdill

Lisa Weber

EXECUTIVE SUMMARY iv

ClinTwin360 Product Categories i

Trial Match i

Digital Health Twin i

Trial Insights ii

Strategic Product Vision ii

PART 1. BUSINESS REQUIREMENTS 1

As-Is | Clinical Trials Today 1

Recruitment 1

Data Collection 2

Trial Retrospectives 3

To-Be | ClinTwin360 4

Trial Match 4

Digital Health Twin Data Collection 5

Trial Insights 6

Functionality 8

Functional Requirements 8

Non Functional Requirements 9

PART 2. TECHNICAL SPECIFICATION & PROTOTYPE 11

Architectural Approach 11

Reference Architecture 11

Application Architecture 11

Software Solution 13

Trial Match 13

Trial Match Admin Portal 13

Trial Match Mobile App 14

Digital Health Twin 15

Trial Insights 18

Data Management 20

Data Flow 20
Partner Application Integration 20
Solution Demonstration 25
Trial Match - Participant App 25
Profile Management 25
Clinical Trial Enrollment 25
Trial Match - Sponsor Mobile App 26
Trial Management 26
Trial Insights 27
Hotspot Analysis 27
PART 3. IMPLEMENTATION PLAN 28
Solution Delivery Roadmap 28
Operationalization 32
Managed Services and Shared Responsibility 32
Balanced Product Teams 33
DevOps 33
Administration and Support Operations 33
Key Non-Functional Operational Components 34
Incident Management 34
Security Operations 34
System Monitoring, Performance and Alerts 35
SLAs 36
User Enablement 38
Participant Engagement 38
Sponsor Engagement 38
User Journey 39
Product Roll-out 40
User Roles 42
Success Metrics 43
Projected Revenue 44
Bibliography 45

Part One 45
Part Two 45
APPENDIX 46
Clinical Trials Glossary 47
Clinical Trial Phase 47
Clinical Trial Recruitment and Adherence 47
Clinical Trial Eligibility Criteria Example 48
Data Lake Reference Architecture 49
Apple Health Expanded Data Categories and Data Types 51
OAuth 2.0 Workflow 52
Partner Application Integration Data Formats 53
GPS Exchange Format (GPX) 53
CDISC Operational Data Model (ODM) 53
Training Center XML 54
Simple Operationalization Model 55
Product Financial Benefits 56
Trial Match 56
Revenue 57
Expenses 57
Digital Health Twin 57
Revenue 58
Expenses 58
Trial Insights 58
Revenue 59
Expenses 59
System Metrics 60

EXECUTIVE SUMMARY

ClinTwin360 Inc. is a mobile app and software as a service (SaaS) firm disrupting the existing clinical trial process. Our goal is to improve the clinical trial process through a data aggregation and integration solution that:

1) Removes participant/trial enrollment inefficiencies through a centralized matching service

2) Improves trial effectiveness by enriching baseline biometric data with contextual data for deep insight into cause/effect and multicollinearity resolution.

3) Optimizes incremental trial execution by introducing data analysis across a wide array of clinical trial and contextual data.

The benefits of ClinTwin360 include enabling sponsor-driven recruitment, the enrichment of clinical trial data with contextual data and the ability to analyze robust clinical, medical and contextual data to support continuous improvement of clinical trials.

ClinTwin360 Product Categories

Trial Match

Analogous to a matchmaking service, identifies and aligns qualifying participants with trial sponsors based on trial scope and participant requirements.

Participant recruitment and enrollment is a $5.9B annual expense and a documented challenge within the clinical trials industry. The initial enrollment phase accounts for a substantial portion of the clinical timeline (30%). Roughly 80% of clinical trials fail to hit deadlines while 11% fail to enroll a single participant. Typically enrollment periods are doubled in order to meet an approved enrollment size.[1,2]

Trial Match centralizes the participant pool, providing a streamlined conduit for trial-participant matching, acceptance and enrollment.

Digital Health Twin

Provides rich contextual clinical trial participant data to clinical trial sponsors.

With *Digital Health Twin*, contextual data such as biometric sensor data, environmental, air quality, and geolocation data provides a frame and substance for point-in-time participant data collected from clinical trial participants during a healthcare professional site visit.

This enables clinical trials to effectively operate on a more complete foundation of relevant data for effective decisions. Trials can “fail fast”, efficiently identify causation as well as efficacy, and uncover

unforeseen/unexpected results or side effects in earlier trial stages, reducing costs from prolonged trial progress.

Trial Insights

Provides retrospective insight for continuous improvements to clinical trials.

Learning is core and fundamental to progress. ClinTwin360's *Trial Insights* provides an analytic capability with a unified platform of contextual data that can enable data scientists to perform trial retrospectives to determine enhancements to clinical trial protocols.

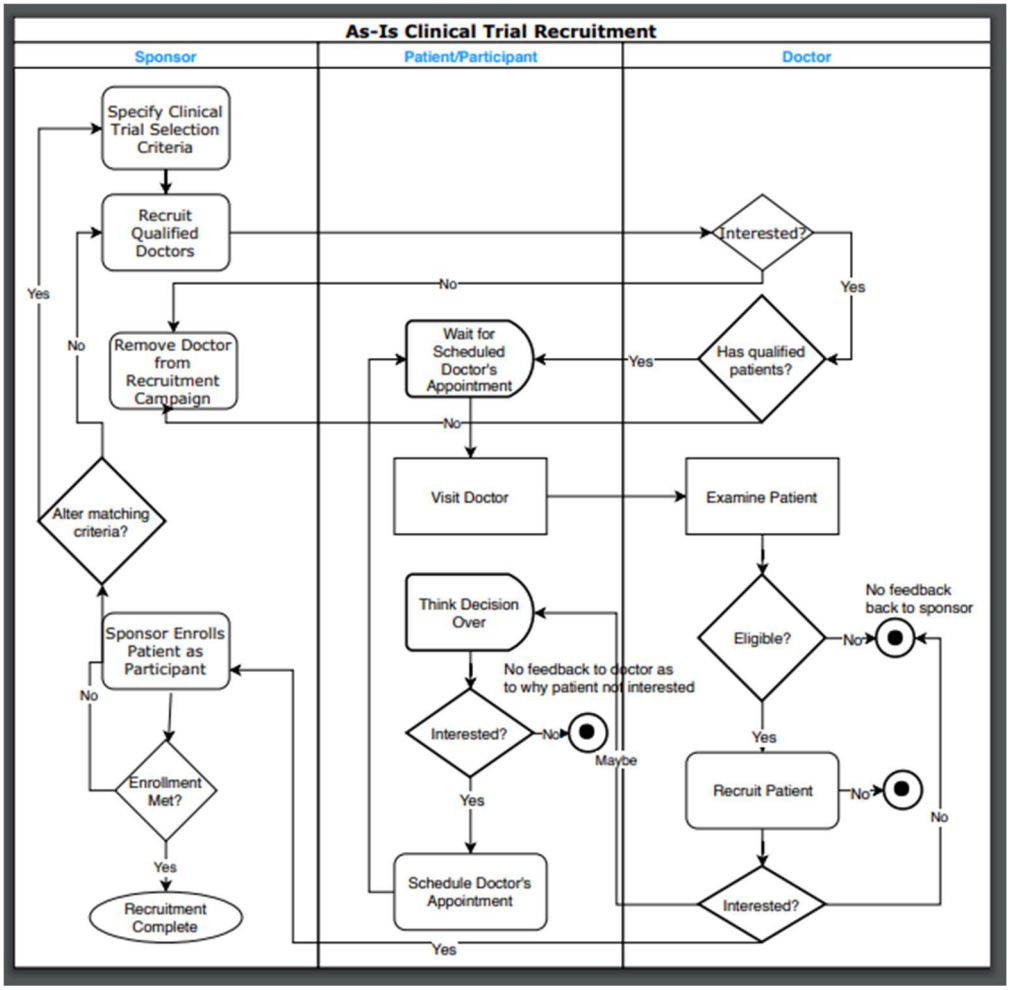
Strategic Product Vision

PART 1. BUSINESS REQUIREMENTS

As-Is | Clinical Trials Today

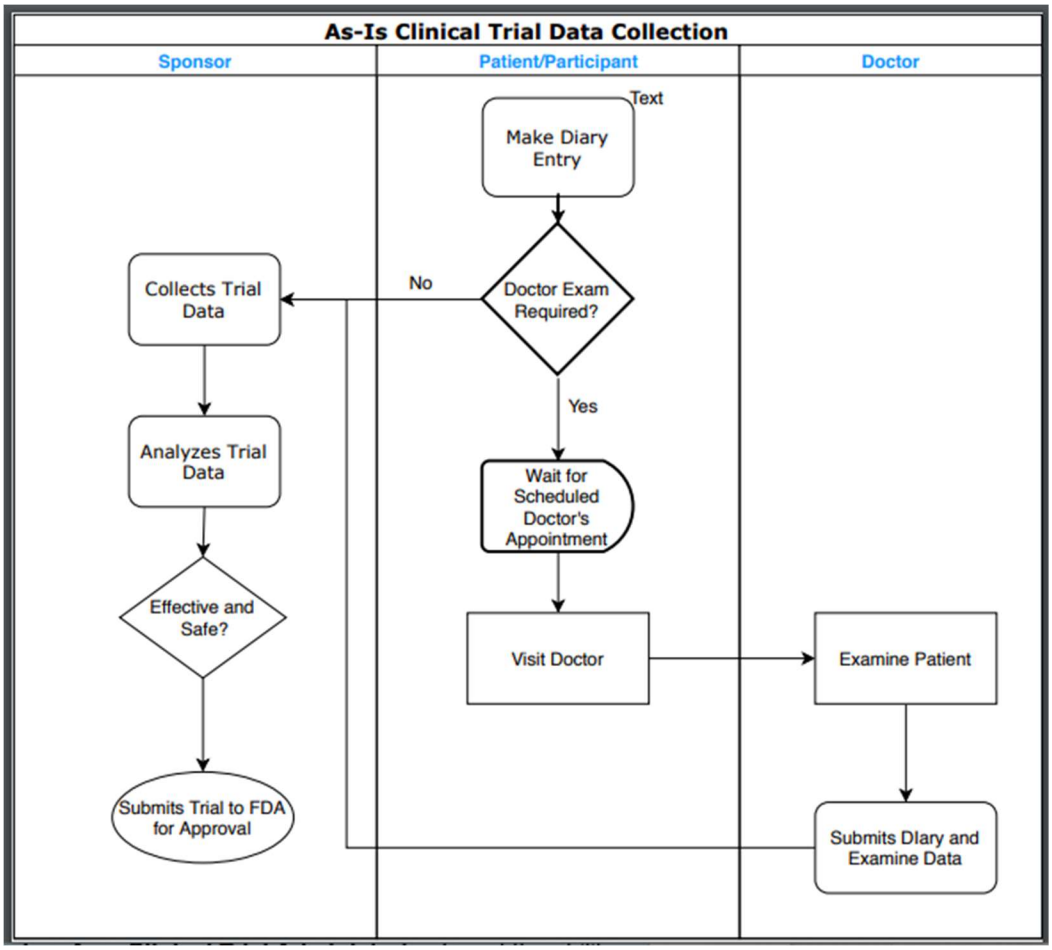
A clinical trial is a medical study initiated by a trial sponsor, typically a pharmaceutical or medical device manufacturing company or a government or health organization. It involves the evaluation of human volunteers who agree to follow a prescribed intervention (medical product, behavior or procedure) over a period of time so that researchers can monitor and record biomedical or health outcomes of the intervention. Based on the current practices that clinical trials use to recruit participants and collect trial data (see Appendix: Clinical Trial Recruitment and Adherence), the current clinical trials process suffers from three major problem areas.

Recruitment



First, a trial can only be initiated once it has successfully recruited the required number of participants as specified in the trial protocol. Research indicates, of the healthcare professionals (HCPs) recruited by the trial sponsor, only 25% end up having access to the needed qualifying participants.[4] This is primarily due to the difficulty with finding participants who not only have the right demographics and biomarkers as specified within the protocol but who are also willing to participate. Today, due to having to rely primarily on first recruiting HCPs who potentially have participants matching the protocol requirements, participant recruitment is an arduous and lengthy process with costs ranging from $15,700 to $26,000 per participant recruited.[3] The trial sponsor underestimating the amount of time that it will take to recruit enough participants to satisfy the trial protocol and doctors overestimating their ability to recruit participants is what contributes to the significant costs.

Data Collection

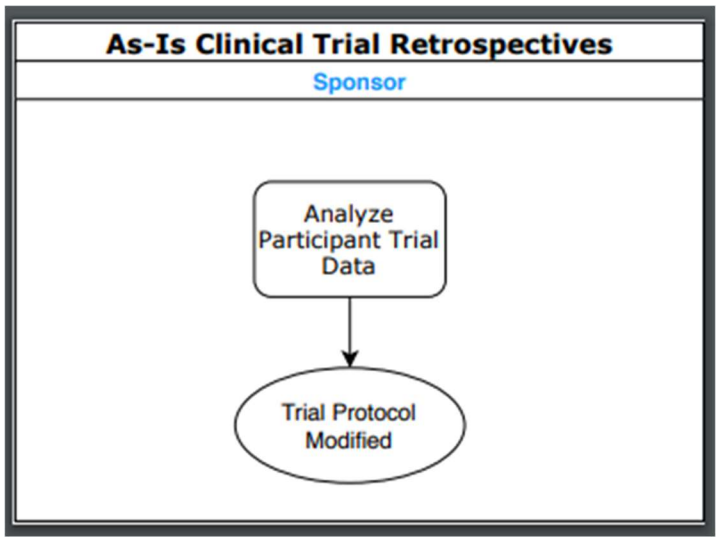


Another key problem area is the trial data itself. The insightfulness of the trial research is constrained by the data captured while running the trial. Today, for the majority of trials, the data collection process is manually performed by the participant or by a HCP at prescribed site visits. While the data captured at these visits can provide needed data points for the trial, manual site data collection poses three significant problems. First, the data points are only representative of the participant's biometric context at a single

point in time, and therefore, are potentially missing context to any external factors that the participant has been subject to throughout the day which could have an impact on the quality of the data being provided. Second, manual data collection is fraught with errors. Relying on participants to keep diaries of daily activities and wellness indicators and remember their prescribed site visits so the information can be communicated to the HCP is heavily dependent on the participants' diligence and is largely subjective in nature. Third, although biometric data collected at site visits is objective in nature, it is costly, accounting for 20-25% of clinical trial costs (approximately $6B per year).[5]

Trial Retrospectives

Finally, the last major challenge is the limited access to comprehensive and contextual trial data analytics to perform retrospectives. Due to the nature of trials today, researchers are limited to the data that is collected during the course of the trial as prescribed by the trial protocol. Performing trial retrospectives, particularly during earlier phase trials, to gain deeper insights is limited to the data collected. Lack of additional ancillary data or contextual data that could have impacted the collected biometrics, limits the researcher's ability to perform optimal continuous improvement on a trial which often leads to inefficient lead times to finding necessary correlations contributing to efficacy and safety.



To-Be | *ClinTwin360*

ClinTwin360 is breaking ground by creating a new market segment that does not currently exist. It is imperative to the success of the company that *ClinTwin360* enable clinical trials to be efficiently recruited, enriched with contextual data, and continuously improved with holistic participant metrics to positively impact current and future clinical trials. *ClinTwin360's* comprehensive solution can be characterized into three distinct components.

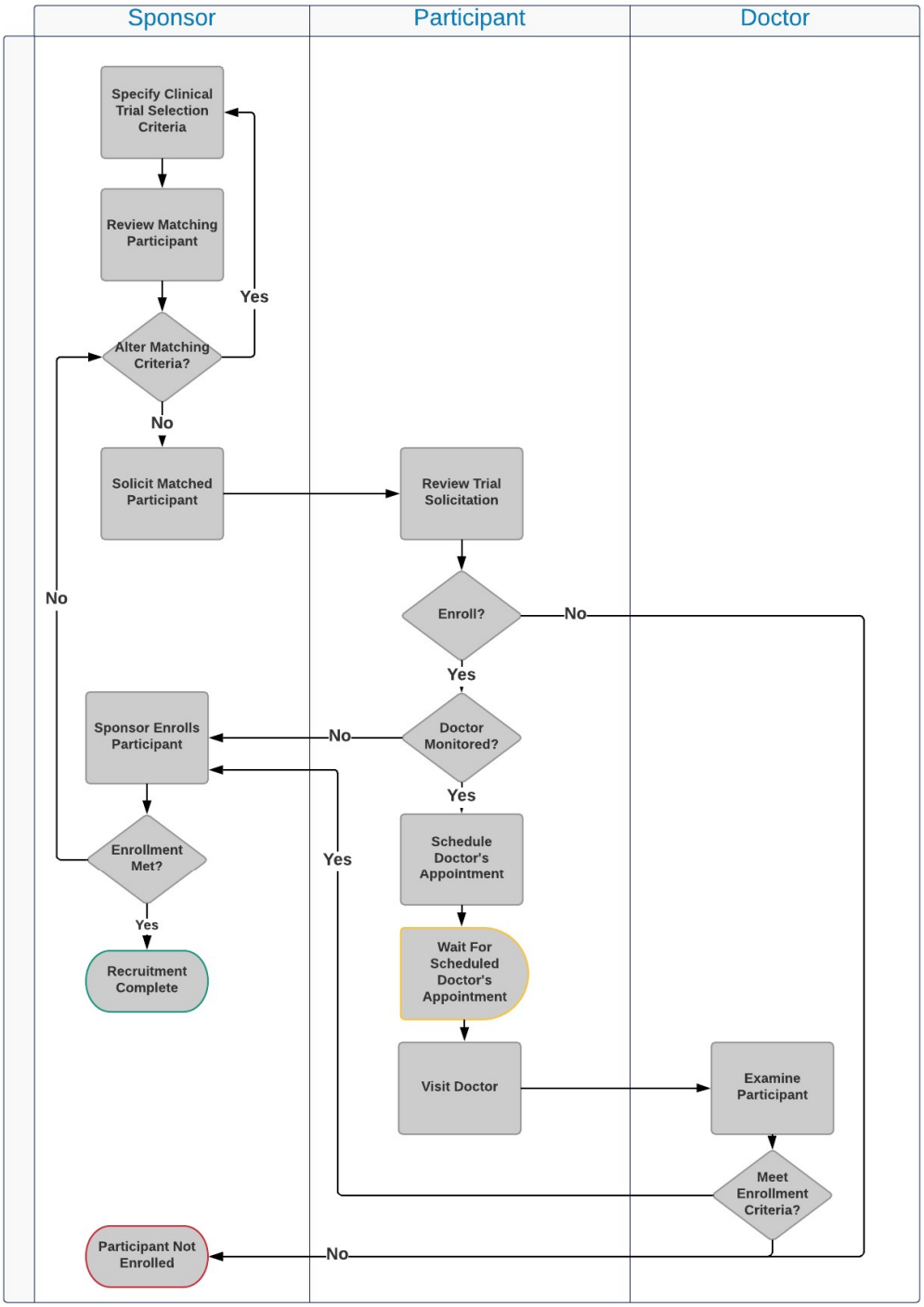
Trial Match

The first component, *Trial Match*, is an activation and management gateway for clinical trial candidates and participants. *Trial Match* provides the following high-level features to the end-user participant:

1) Service registration, verification, activation, and terms of acceptance
2) Authorization for third party data integration
3) Trial recruitment and enrollment status, schedule and information
4) Push notifications and messaging for system and trial communication

Trial Match is a key source of *ClinTwin360*'s value proposition. The functionality provides a direct channel between a trial and an ever-growing pool of prospective participants, removing complexity from the enrollment and registration process. A participating trial sponsor defines participant eligibility criteria and receives access to qualifying participants. This eliminates participant prospecting inefficiencies while introducing a seamless participant enrollment experience to facilitate acquisition, retention and overall quality.

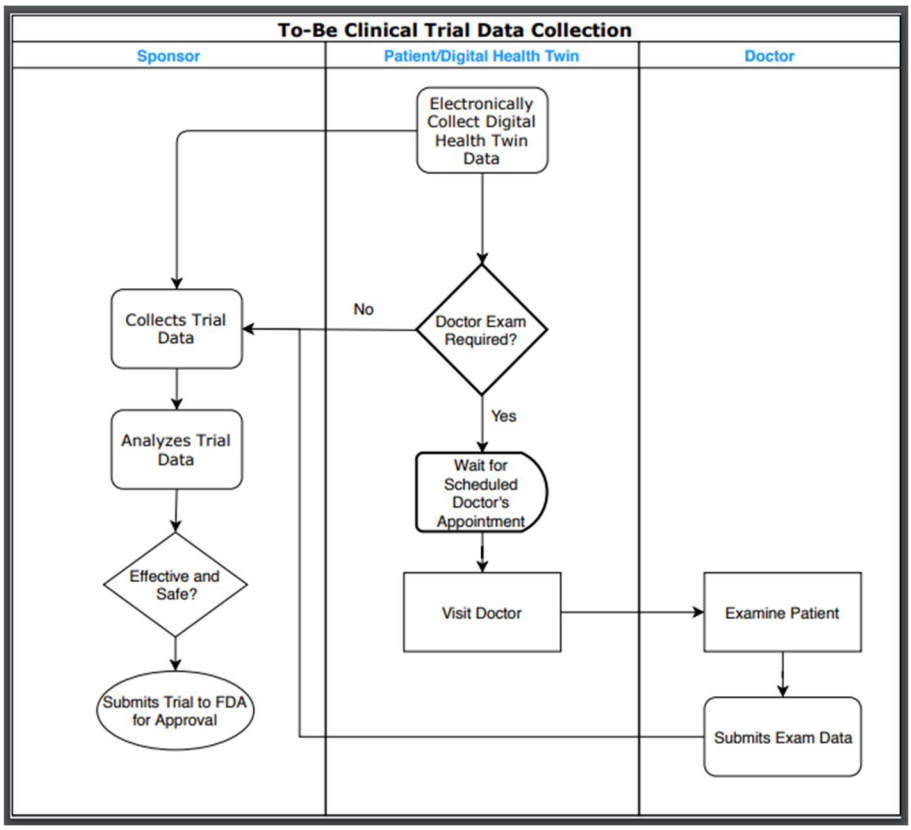
Trial Match also provides an integrated ecosystem for the collection and sharing of contextual data. Participants authenticate and approve the use of qualifying IoT and mobile app accounts as part of the setup and enrollment process. Approved services such as Apple Health, Fitbit, Strava and Peloton provide transformative real-time insight into environmental, behavioral and activity-based contributors to illustrate a true picture of a participant, beyond a point-in-time snapshot of a sponsor's in-scope biometric data. Through the app, participants can select which services they use, authenticate and define scope of privileged access, and share data with an associated trial through the *ClinTwin360* ecosystem. Trials may also distribute medical devices which can be ingested into the ecosystem.



Digital Health Twin Data Collection

The second component, *Digital Health Twin*, is *ClinTwin360's* enriched data collection and aggregation platform. *Digital Health Twin* securely sources a participant's IoT and mobile app event data as well as geolocational data, ingests it for processing, and delivers it to a sponsor's subscribing clinical trial data collection platform. Rich, multi-sourced contextual data - encompassing areas such as biometrics, fitness, air-quality, GIS, traffic and weather data - is combined to construct a participant's digital twin for rapid data-

driven insight. Over time and across trials, a participant's digital twin - a virtual manifestation of the participant - evolves based on the participant's changing health and wellness.

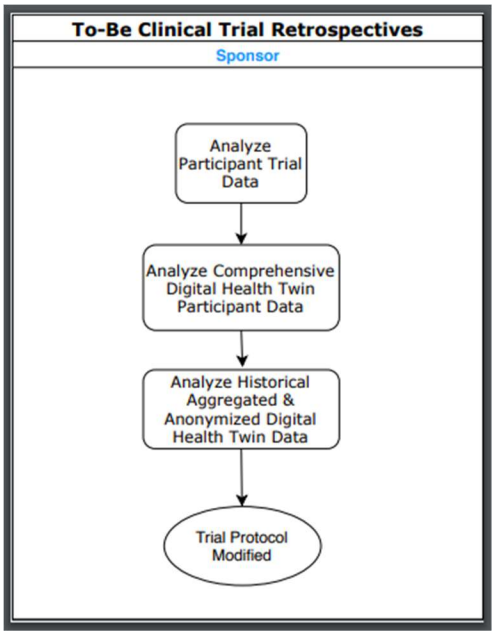


Trial Insights

The final component of *ClinTwin360*, *Trial Insights*, provides a single source for accessing anonymized raw trial participant data (proprietary to the trial sponsor) as well as anonymized and/or aggregated *Digital Health Twin* data that can be analyzed to aid in continuous improvement of on-going and future trials. With industry-leading encryption and security standards, sponsors gain privileged access to their trial data across any appropriate format. The company is empowered to meet business goals through gained insights from the platform's rich analytical capabilities.

As trial and supplemental *Digital Health Twin* data is available during and after a respective trial, decisions and improvements can be made immediately. Decisions related to efficacy and causality, or the lack thereof, can take place during a trial allowing a trial to pivot or "fail-fast", greatly reducing wasted time and costs allowing for operational and effectiveness improvements. Sponsor administrators can configure integrations back into their existing systems, decide their data granularity, format, and delivery mechanism.

Furthermore, through the *Trial Insights* portal, sponsors can create targeted outreach campaigns via the *Trial Match* app to recruit participants matching desired criteria for upcoming trials. The platform can find the best matches and notify participants about the opportunity and how to register.



A key aspect of the “to-be” state of *ClinTwin360* is that the interaction between participant and the clinical trial does not change. Clinical trials have very stringent regulatory requirements that *ClinTwin360* intentionally is not initially interested in disrupting. By limiting this scope, *ClinTwin360* can drive digital transformation in this traditionally conservative industry which can be difficult to break into as a new company.

Initially sponsors will join *ClinTwin360’s* platform through outreach and because of the opportunities presented with access to data. Over time, *ClinTwin360’s* participant user-base will reach critical mass and companies will join and continue to stay engaged because it is the most efficient and reliable place to find willing-and-able participants.

Functionality

Functional Requirements

Epic | Match qualified participants to clinical trials

User Story | As a Clinical Study Administrator, I want the ability to manage participant recruitment attribution so that I can specify trial participant matching criteria as specified within my clinical trial protocol.

Acceptance Criteria

- Select the participant criteria attributes used to filter prospective candidates across participant and trial criteria
- Define contextualized data preference (sources, services, types) and requirements for potential participation
- Define and save participant requirements for trials

User Story | As a Clinical Trial Administrator, I want the ability to directly solicit participants whose biometric, geolocation and contextual data matches my trial protocol eligibility criteria so that I can reduce the participant recruitment and enrollment timeline.

Acceptance Criteria

- Engage a pool of approved participants for enrollment
- Solicit additional prospects for inclusion in a trial
- Access preferred communication details within a participant profile
- Deliver in-app messaging to prospective participants

User Story | As a Clinical Study Administrator, I want the ability to anonymously review and approve a potential pool of qualified participants that meet my requirements before enrolling them in my trial.

Acceptance Criteria

- Review participant matching parameters and adjust criteria to widen and narrow the pool at any time of enrollment without impacting enrolled participants
- Approve and remove anonymous candidates from my pool of prospective candidates before initiating a matching workflow for acceptance of enrollment.

User Story | As a trial match participant, I want the ability to review upcoming clinical trials so that I can make informed enrollment decisions and receive notifications for current enrollment as well as new opportunities, based on my biometric, geolocation and contextual data.

Acceptance Criteria

- Manage a profile including personal information and communication preferences
- Authorize third-party integrations for use with clinical trial matching
- Receive notifications regarding prospective, current and historical trial participation

- Review app privacy and legal info

Epic | Provide a clinical trial sponsor rich contextual data

User Story | As a clinical trial administrator, I want biometric, geolocation and contextual participant data ingested into my clinical trial, so I have a more holistic representation of a participant's health.

Acceptance Criteria

- Receive contextual data during the life of the defined trial phase
- Integrate/Ingest/Extract/Transform/Load data from clinical study participant approved sources into my EDC system
- End-to-end data security and anonymity throughout the collection, aggregation and integration workflow

Epic | Provide a central platform for retrospective analysis and continuous improvement

User Story | As a clinical trial data scientist, I want the ability to query participant and trial data so that I can perform retrospectives to find patterns and correlations to continuously improve my clinical trial protocol.

Acceptance Criteria

- Secure portal which provides access for sponsors to centrally manage their contextual data integration requirements as well as connect to current and historical clinical data
- Ability to export data

User Story | As a clinical trial administrator, I want the ability to manage clinical trials privately across every phase of a trial as well as during recruitment.

Acceptance Criteria

- Permission based portal with clinical trial management solution
- Current clinical trial roll-up visualization for high level tracking of contextual data-specific metrics
- Current clinical trial management for status (active, new, ended) management and auto-generated alerts based on trial cadence, schedule changes or status change
- Historical ledger of conducted clinical trials as well as data connection, integration and export capabilities
- Access to help documentation, support, legal and defined SLAs
- Onboarding account management documentation and best practices artifacts repository

Non Functional Requirements

Availability and SLA | The service (as required by standard SLA) must maintain a four nines availability percentage outside of any scheduled maintenance windows for related enhancements.

Data integrity | Participant and trial-generated data that passes through the ClinTwin360 ecosystem must maintain end-to-end accuracy and consistency among sources and destinations. Data quality, and validation must ensure data maintains accuracy and avoid unintended change throughout a data lifecycle

Usability | The user experience across interfaces must be consistent, intuitive and optimized for effective and efficient management of clinical data for all participants and administrative stakeholders. Ease of use must be established and maintained through usability engineering and testing

Compatibility and Interoperability | Web applications must be compatible with all currently supported industry standard browsers. All web applications must account for mobile-first design to create a device-agnostic experience. The native mobile application must be compatible with Android and iOS platforms and allow for backwards compatibility as well as access for all requisite device features. The data aggregation engine must be compatible with industry standard API protocols, architectural styles to integrate 3rd party contextual data and provide integration for pharmaceutical company business systems

Extensibility | The system must be extensible to allow for future integrations for contextual data integration to meet company needs and evolving 3rd party solutions without impacting the underlying system functions

Security Compliance and Best Practices | ClinTwin 360 must adhere to any and all PII, HIPAA, PCI compliance, privacy and security best practices such as OWASP as they come into scope.

PART 2. TECHNICAL SPECIFICATION & PROTOTYPE

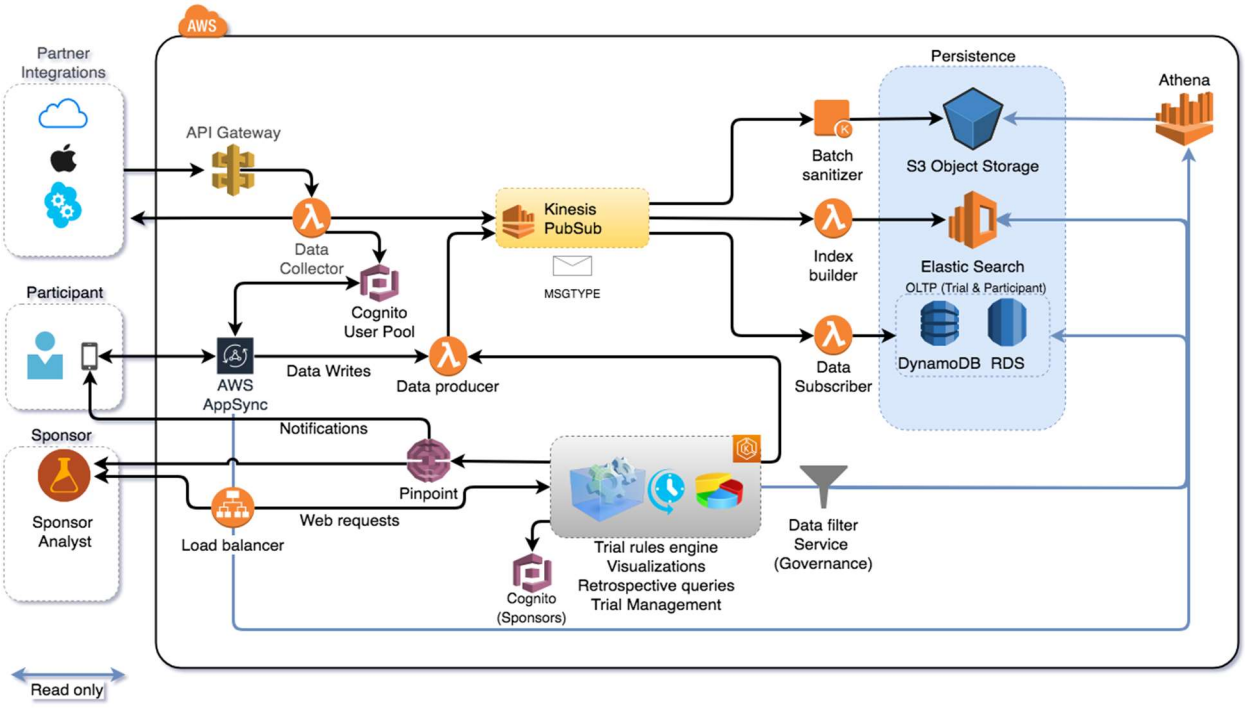
Architectural Approach

Reference Architecture

The *ClinTwin360* ecosystem's foundation is the *Digital Health Twin* data ingested from internal and external, structured, semi-structured and unstructured sources. To enable the *Digital Health Twin* data to support a wide range of trial recruitment, data capture, analysis and retrospective requirements, an agile AWS data lake storage reference architecture (see Appendix: Data Lake Reference Architecture) is used to support raw data storage with definitions and structures only defined upon usage i.e. schema-on-read. This architectural approach allows for ultimate flexibility as well as increased speeds for extracting, loading and working with the data.[17,18, 19]

Application Architecture

ClinTwin360's application architecture leverages loosely coupled services that can be used securely across all three of its platforms, *Digital Health Twin*, *Trial Match* and *Trial Insights*, as well as externally to ingest partner application data.



ClinTwin360's applications leverage a common data lake within the *Digital Health Twin* platform that enables trial participant matching within *Trial Match*, trial analytics within *Trial Insights* and clinical trial electronic data capture integration via the published API.

Data is produced consistently through a PubSub messaging system, at which point one or more consumer services event-source, transform and persist relevant data appropriate for the data-store that can be accessed in various ways across ClinTwin360 products. This includes object storage, relational, unstructured data, and indexed data.

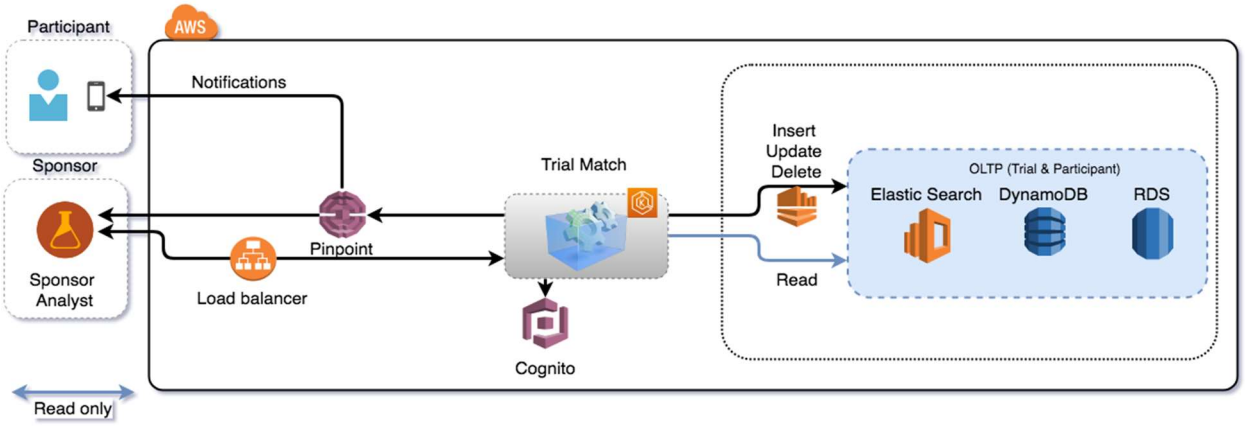
As the ClinTwin architecture evolves and products mature, new functionality may warrant new storage or enrichment technologies. To onboard additional data-stores, like RedShift, or HDFS, a new consumer service can subscribe to Kinesis and start listening to messages without complex integration work.

Software Solution

Trial Match

Trial Match Admin Portal

The *Trial Match* admin portal is a secure web application used by sponsors to manage trial recruitment and enrolled participants through the following workflow:



Clinical Trial Management | Sponsors register each clinical trial and indicate its eligibility criteria. The data is stored in the Trial RDS database (see Appendix: Clinical Trial Glossary | Clinical Trial Eligibility Criteria Example for example eligibility criteria data).

Clinical Trial Notifications | Sponsors setup and manage targeted messaging and notifications to app users through a user-friendly admin campaign and communications interface, which utilizes AWS' Pinpoint API for push service, email, text-message and other types of notifications.[9]

Clinical Trial Participant Recruitment and Monitoring | Sponsors have the ability to manage eligible participants through the recruitment process as well as monitor active participants for adherence to the trial protocol. If for some reason the participant falls out of adherence, the sponsor can remove the participant from the trial. With consideration to PII and PHI sensitivity, *Trial Match* takes care to only expose data attributes that are relevant to patient/trial matching as authorized by the user as well as trial protocol data while keeping secure the user's comprehensive digital twin profile managed within the *Digital Health Twin* product.

Higher sophistication for targeted messaging and alert campaign management features are provided through Amazon Pinpoint. Features and capabilities include:

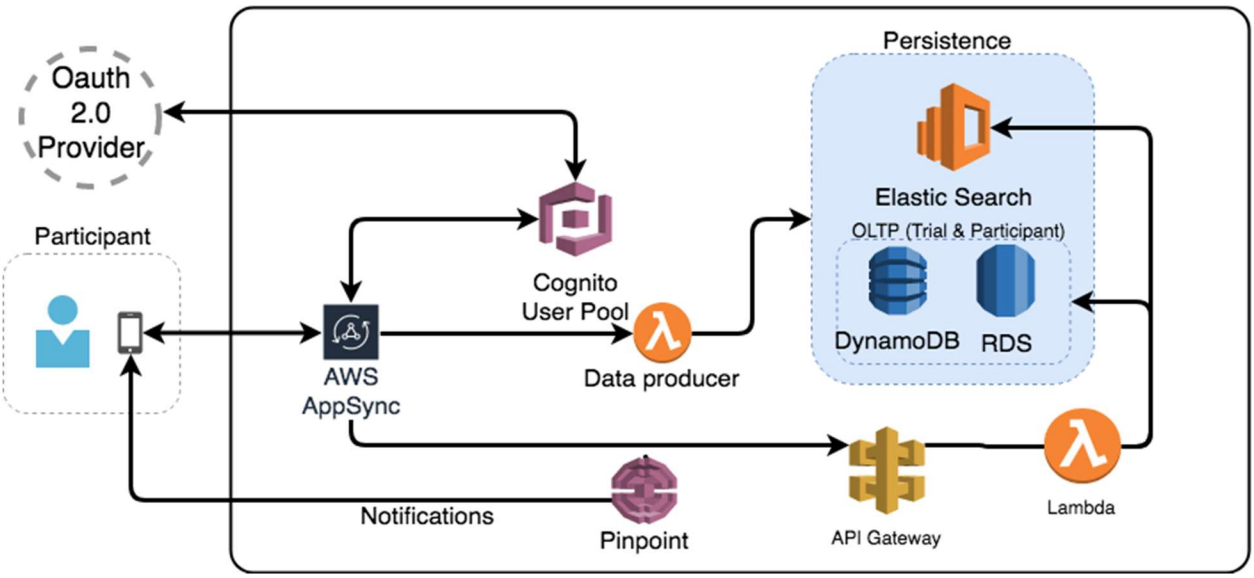
- Usage and engagement analytics
- Audience segmentation
- Messaging templates and scheduled communication campaigns across email, SMS and push notifications

- REST API

Amazon Cognito is utilized with Amazon Pinpoint to provide analytics for defined user pools to manage campaigns based on participant attributes defined within the iOS operating system and implemented using AWS' respective SDKs.[24] [25]

By providing a direct connection between clinical trial administrators and a pool of prospective and active participants, *Trial Match* is able to reduce inefficiencies surrounding trial enrollment and participant defection, while increasing the likelihood of aligned candidates based on standardized participant requirements as well as more comprehensive and contextually enriched participant data.

Trial Match Mobile App



The *Trial Match* mobile consumer app, built for iOS mobile devices, is the platform within the *ClinTwin360* ecosystem that matches participants to actively recruiting trials through the following workflow:

Participant Registration and Profile Population | Participants register within the application and enter demographic profile data as well as authorize additional profile data to be pulled from partner applications (e.g. Fitbit, Peloton, Apple Health, etc.) that they would like made available for use in matching themselves to recruiting clinical trials. *Trial Match* registers the participant in the Participant database.

Partner Application Authorization | *Trial Match* sends the participant profile information and partner application authorization data to the *Digital Health Twin* platform utilizing Lambda and API Gateway services to initiate partner integration (see *Digital Health Twin* for details concerning Participant Partner Application Integration Authorization and Partner Application Integration Data Ingestion).

Clinical Trial Matching | The *Trial Match* Rules Engine runs against the Trial RDS to retrieve the trial eligibility criteria for each active recruiting trial and formulates and sends an analytical query via Lambda and API Gateway services to *Digital Health Twin* to request app participants who match the eligibility criteria.

Clinical Trial Match Notification | Participants who successfully match to actively recruiting trials receive in-app notifications alerting them to the matched clinical trials. Participant push notification is provided by SNS. Participants enroll and subscribe to trial-specific topics in order to receive future SNS messages as well as two-way communications from the Admin Web Portal during trial participation.

Clinical Trial Enrollment | Participants alerted to matched trials review the trials and indicate whether or not they wish to enroll. If enrollment is contingent upon the oversight by a healthcare professional (HCP), they have the ability to receive a notification within the app instructing them how to connect with an approved HCP in their area.

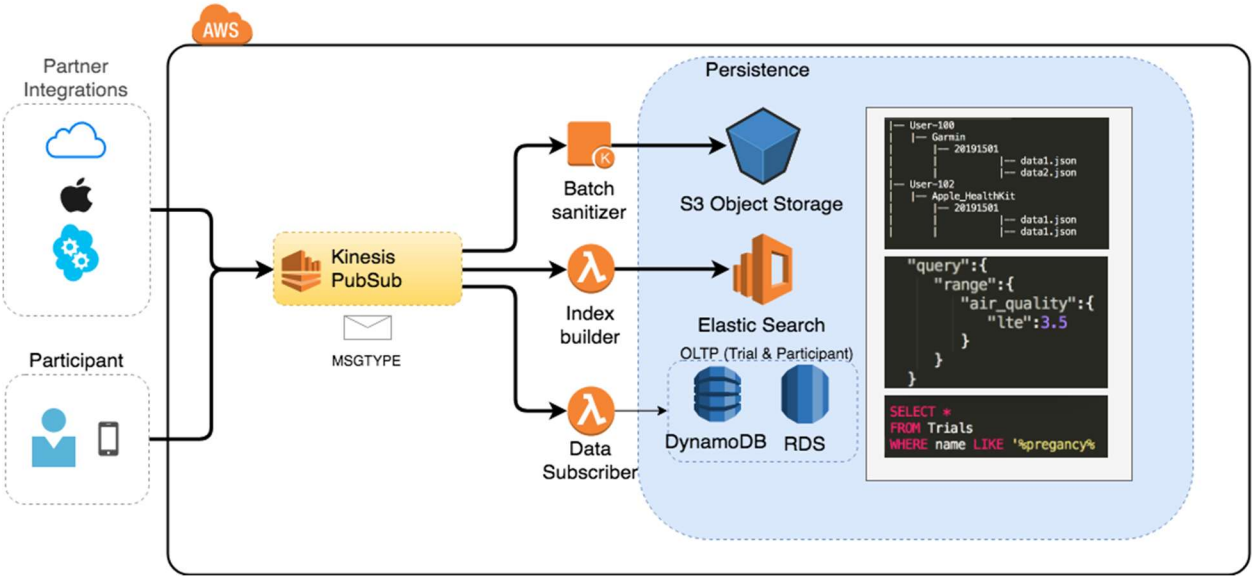
Clinical Trial Participation | For the duration of the trial, the app sends notifications to the user related to the trial such as appointment and drug adherence reminders as well as any sponsor generated messages. Responses to the notifications are tracked for trial adherence and stored in the Participant RDS related to each trial.

***Trial Match* - App Development Considerations** | To maintain platform/provider consistency, the *Trial Match* app utilizes the AWS Amplify Framework and AppSync Managed Service.

- **AWS Amplify** | Unified framework and toolchain of platform services to build mobile applications on AWS. Amplify relies on opinionated libraries, UI components, and a CLI to build the integrated backend for the *Trial Match* iOS native app.[22]
- **AWS AppSync** | Serverless backend for mobile and web applications maintains app data in real time across participant devices. *Trial Match* relies on the AWS AppSync SDK and Apollo client.

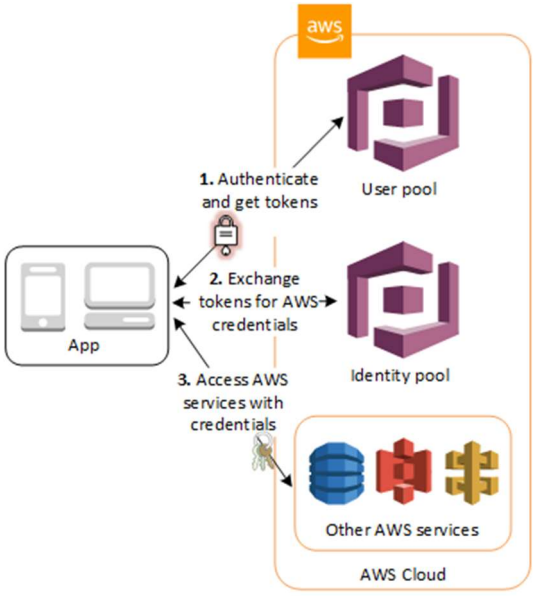
Digital Health Twin

The *Digital Health Twin* platform serves as a data lake repository - a platform for each participant's digital health twin dataset comprised of their *Trial Match* profile data as well as any partner application integration data (e.g. Apple Health, Garmin, Strava, Waze/Google Maps, etc.) the user has authorized and any integrated geolocation contextual data (e.g. environmental, socio-economic, transportation, etc.).



Participant Partner Application Integration Authorization | Upon receiving a participant partner application integration authorization request from *Trial Match*, the *Digital Health Twin* platform manages scalable accessibility, standards-based authentication and federated identity management (including facility for OpenID Connect, using REST based messaging and JSON web tokens within an OAuth2 framework) with the application partner using AWS Cognito. AWS Cognito ensures:

- Social and enterprise identity federation
- Standards-based authentication
- Encryption of data-at-rest and in-transit
- HIPAA eligible compliance

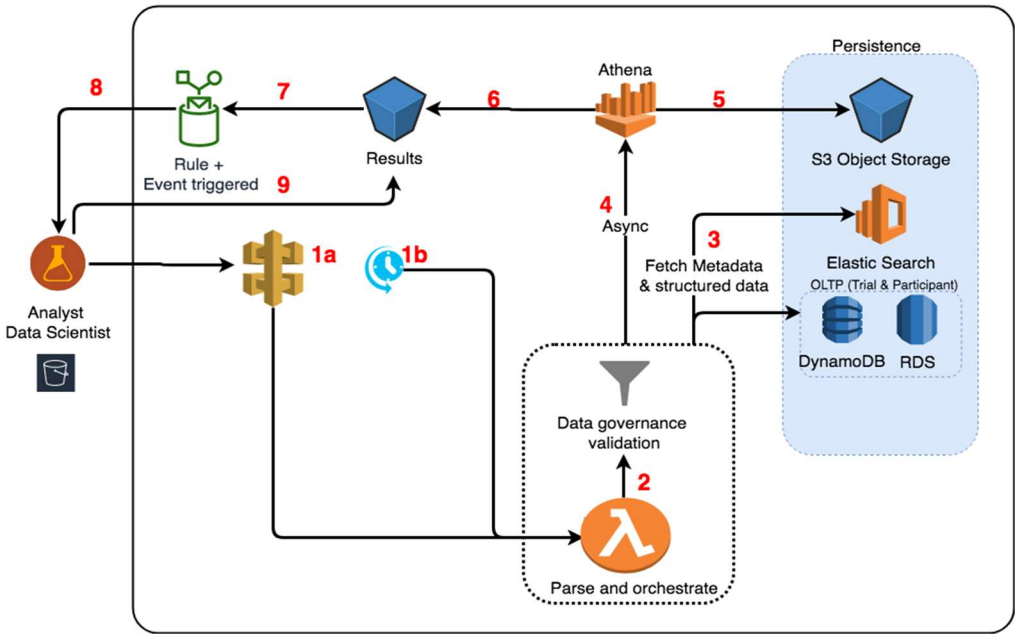


Partner Application Integration Data Ingestion | Once authenticated and authorized to pull the partner application integration data, the disparate structured and unstructured data is ingested into the *Digital*

Health Twin platform data lake as follows (see Appendix: Partner Application Integration Data Formats for examples):

- **Acquire |** AWS Lambda "data collectors" collect partner integration data on behalf of participants. Collectors also collect general purpose contextual data like weather, air quality and population. write to Amazon Kinesis.
- **Store |** Kinesis data consumerers parse and catalog metadata in ElasticSearch to ensure data in the data lake discoverable (i.e. searchable and queryable in a single view), as well as enable it for ETL in preparation for analysis via *Trial Insights* or for external data extraction to Clinical Trial Electronic Data Capture Integration. Data is also PUT into S3 objects which allows a schema-on-read S3 content buckets. This is possible because data-collectors produce data in a consistent format that can be understood by Athena queries.
- **Record |** The metadata, such as the participant from which the data was generated, is loaded into the ElasticSearch service and/or DynamoDB to handle on-demand and scheduled analytic requests to retrieve the data.

Clinical Trial Electronic Data Capture Integration | Trials that have authorized data collection origination from the *Digital Health Twin* platform have scheduled jobs that run to extract and normalize the specified data to conform to the clinical trial data exchange format governed by the following workflow:



- **Request |** A trial extract schedule or Sponsor invoked POST request is submitted within the *Trial Match* mobile application. The request specifies the digital health twin data to process and/or transform per the trial data collection specifications to generate the data manifest.

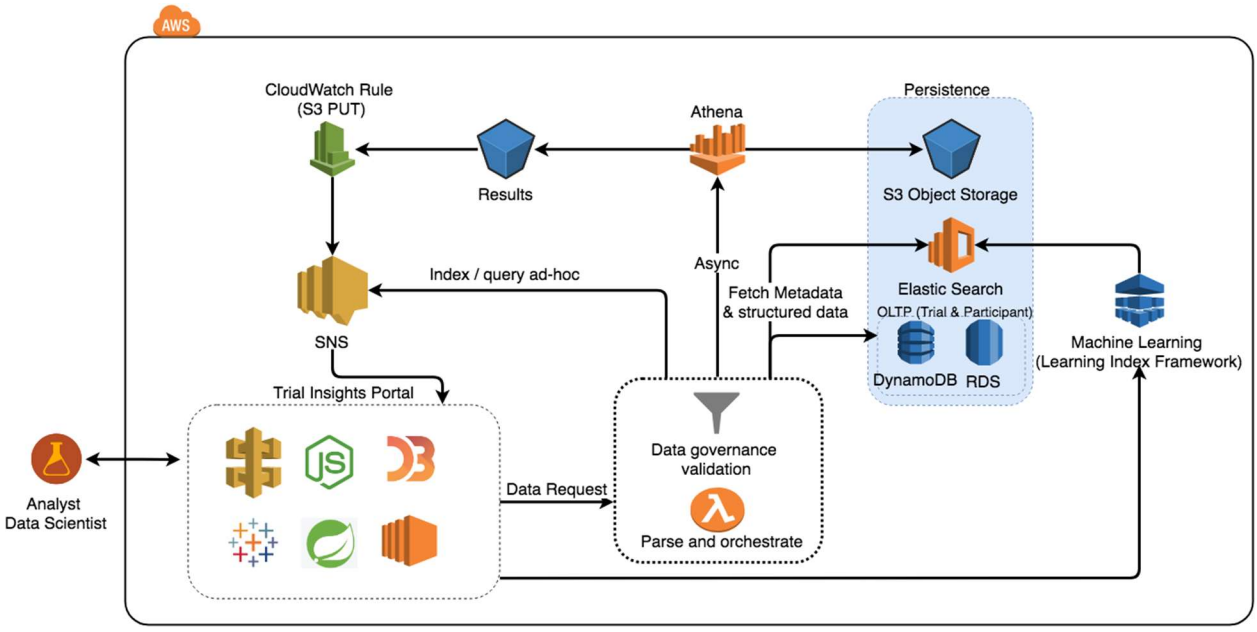
- **Orchestrate |** A Lambda function queries the data catalog generated upon the data load within the ElasticSearch and/or DynamoDB service and builds an Athena query if the requested data is not part of the indexed metadata. The Athena query is then executed asynchronously.
- **Extract & Transform |** The data is extracted, processed and/or transformed using the computed.
- **Load |** The result set of the transformed data is loaded in S3.
- **Distribute |** The result set S3 object creation triggers an event which spawns a notification to alert the requester that the data is available. The result set may be accessed in a variety of ways, depending on how the trial sponsor.

Trial Insights

The *Trial Insights* platform provides a secure web interface for sponsors to engage with the *Digital Health Twin* data via analytical cloud services that perform heavy compute functionality to provide query results within the *Digital Health Twin* platform that can be extracted and viewed within the *Trial Insights* business intelligence application. SNS/Pinpoint notification services can be configured through the portal for intelligent event-driven alerts and communications concerning active trials.[9]

Trial Retrospective Query Request | To enable trial analysis against active and historical trials, data associated with a trial as well as any contextual geolocation data is made available within *Trial Insights* for query and analysis utilizing the Secure by Design architectural pattern.

Secure by Design | To enforce ClinTwin360's data governance model established by the group's security team, role based access control checks are validated before a query is issued to one of the tiers.



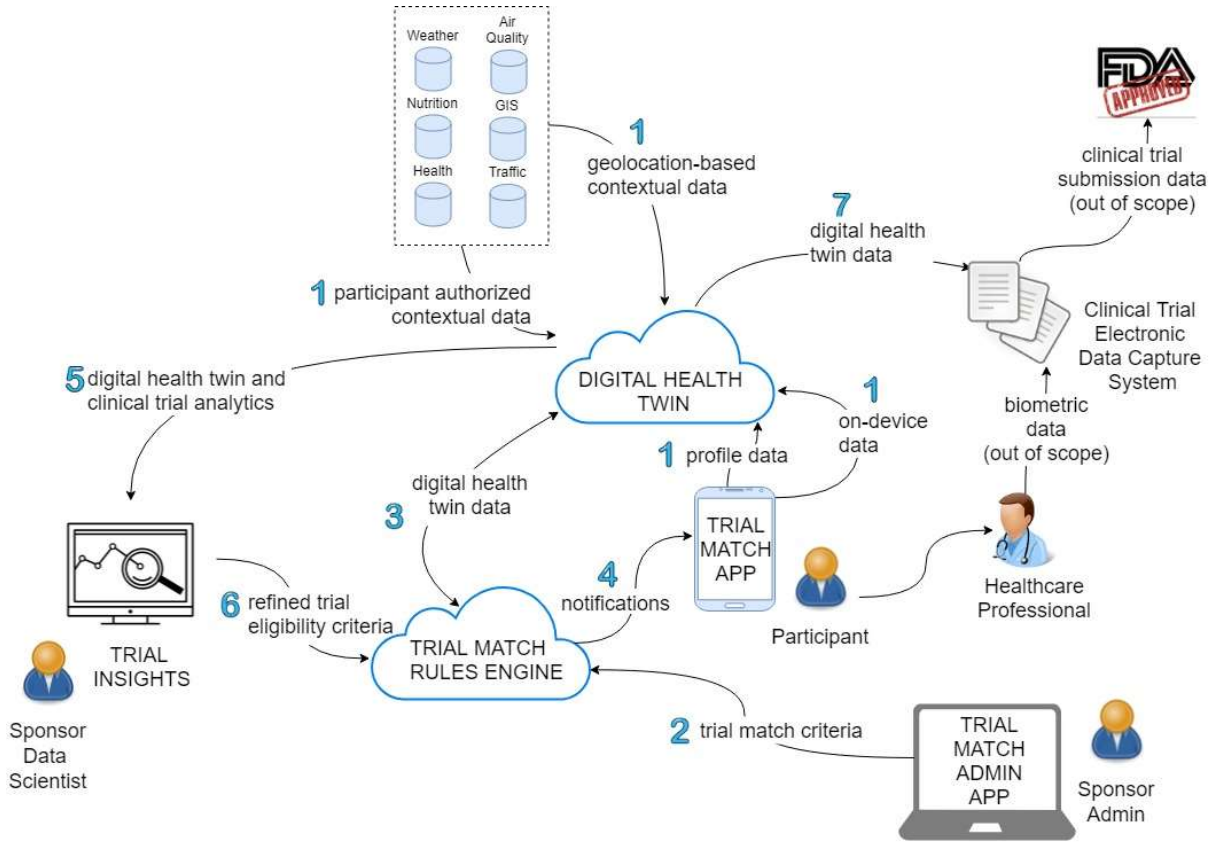
- **Query |** A user initiates a trial based query (e.g. number, age and gender of participants who live in humid vs. arid climate and indicated migraine relief as unintended side-effect).

- **Orchestrate |** The manifest is passed to the Lambda function responsible for the orchestration of the workflow to process the manifest data.
- **Build |** A Lambda function queries the data catalog generated upon the data load within the ElasticSearch and/or DynamoDB service and builds a manifest with the location of the data requested (e.g. S3 bucket, etc.). This step also enforces access control policies.
- **Analyze |** The manifest is passed to downstream Lambda functions which orchestrate the data query request for analysis.
- **Compute/Extract |** The analysis is contingent on the type of query requested: Athena is utilized for population-scale genomics.
- **Load/Notify |** Results from each analysis are loaded into S3 as transformed data when an asynchronous complex query was executed. An S3 Object PUT event will then trigger an SNS notification to alert the originating request service that the results are ready. In the event that the data is already indexed, the location to that index is returned to the caller on the “request-path”.
- **Visualize |** The result set is visualized in *Trial Insights*’ dashboard and query result interface. Additionally, the sponsor can utilize Athena directly, an interactive query service that enables data analysis using standard SQL against S3 bucket objects, to perform ad-hoc queries against the transformed data set.
- **Learn |** Queries that are executed frequently can be pre-materialized and indexed for faster retrieval. This algorithm for determining this is referred to as a caching predictive model.[26]

Data Management

Data Flow

The *ClinTwin360* data ecosystem is centered around the digital health twin data set, a contextually accurate digital representation of *Trial Match* users constructed from user managed profile data and on-device app data (e.g. Apple Health) and medical device sensor data, partner application contextual data (e.g. Fitbit, Strava, MyFitnessPal, etc.) as authorized by each user and geolocation-based contextual data (e.g. weather, traffic, air quality, pollen counts, etc.) (Flow 1). The *Digital Health Twin* platform hosts the digital health twin big data set and enables its use within the *Trial Match* platform to determine trial eligibility matching (Flow 2 and 3), as well as its use within the *Trial Insights* platform to analyze clinical trials (Flow 5). Outcomes from *Trial Insights* are made available to be ingested into trial matching criteria for continuous improvement within the recruitment process (Flow 6). Additionally, the data is available for consumption by clinical trial electronic data capture systems as a complement to the traditional healthcare professional collected biometrics data (Flow 7).



Partner Application Integration

Since *ClinTwin360* is not in the business of creating IoT devices or sensors that emit data, it is essential that data integration is a technical strength of the organization. To do this, the data ingestion pipeline (Flow 1) will follow a decoupled, extensible architecture that allows all day-one integration partners to be

onboarded with minimal effort, and allows the flexibility to onboard additional partners at any point using reusable patterns.

The most efficient way to integrate with *ClinTwin360's* partners is to leverage their already built open APIs. For example, Fitbit, and Peloton provide Consumer APIs that can be leveraged with little coordination with integration partners' development teams and can be called on behalf of participants via *ClinTwin360's* cloud infrastructure. *ClinTwin360's* ingestion pipeline shall be composed of concurrent serverless instances collecting participant data from each partner integration the participant has authorized. Each integration has a collector integration code-base tailored to each partner's data API scheme. At some frequency, participant data is either fetched or pushed to/from the collector's serverless tier. *ClinTwin360's* ingestion integration cost is proportional to the collection frequency and number of participants in the system with activated integrations.

A typical partner integration onboarding process can be generalized into three distinct phases:

1. *ClinTwin360* register's a client service-account for API requests on behalf of authenticated participants.
    a. Optional: *ClinTwin360* secures and persists ClientID and credentials / keys.
    b. Optional: *ClinTwin360* provides secure URL for partner to send data to
    c. Optional: API rate-limiting numbers are negotiated

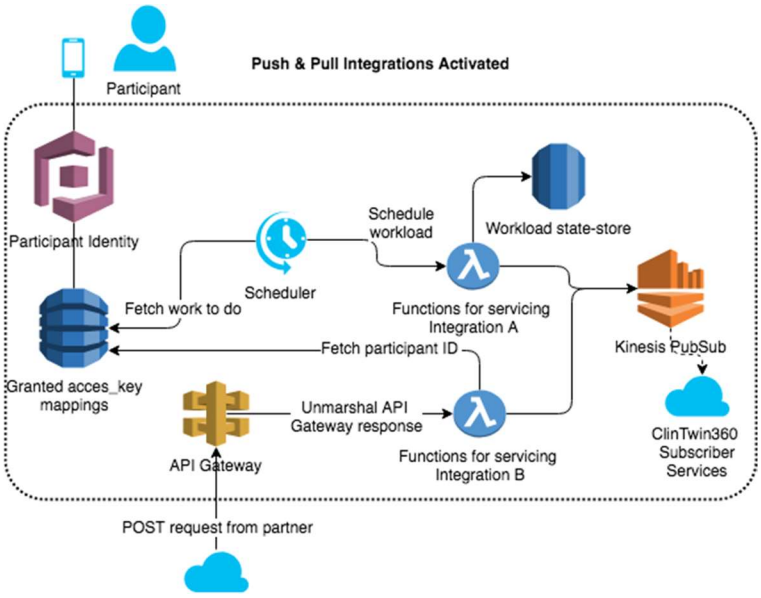
2. · Integrate participant authentication & authorization workflow
    a. Add integration toggle to Mobile App
    b. Store & secure participant access_keys, if necessary

3. Develop stateless data-collector code-base
    a. Poll-based API collector, based on configurable interval
    b. Push-based API gateway, always available to service incoming requests

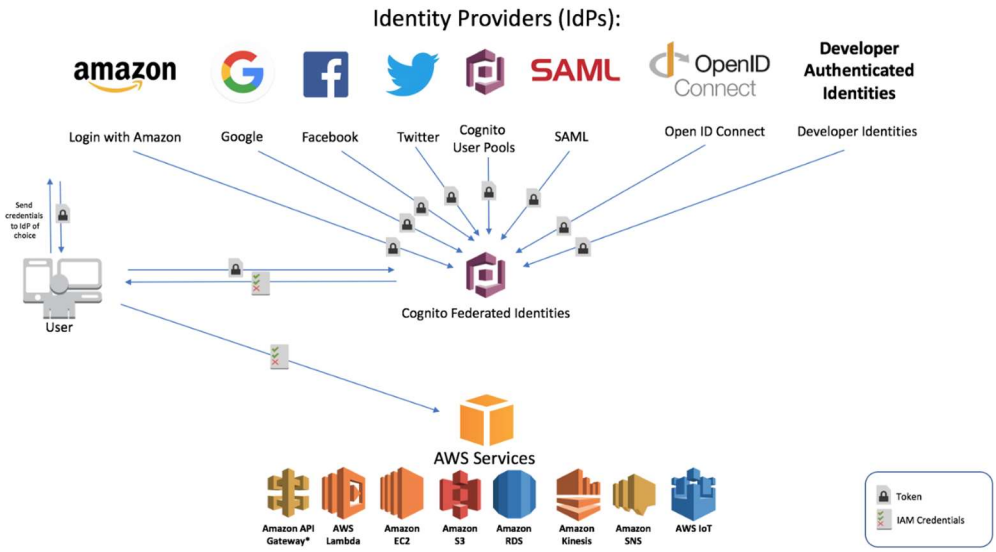
The key to managing homogeneous data-collector types is by coercing data into a common message format that can enter the *ClinTwin360 Digital Health Twin* front-door - a Kinesis PubSub system. Each collected message can be distilled into the following attributes and be processed to subscribers, regardless of what the partner's API response or format is:

- Participant identity
- Integration partner identity
- Timestamp of action (not to be confused with ingestion timestamp)
- Numeric metric value

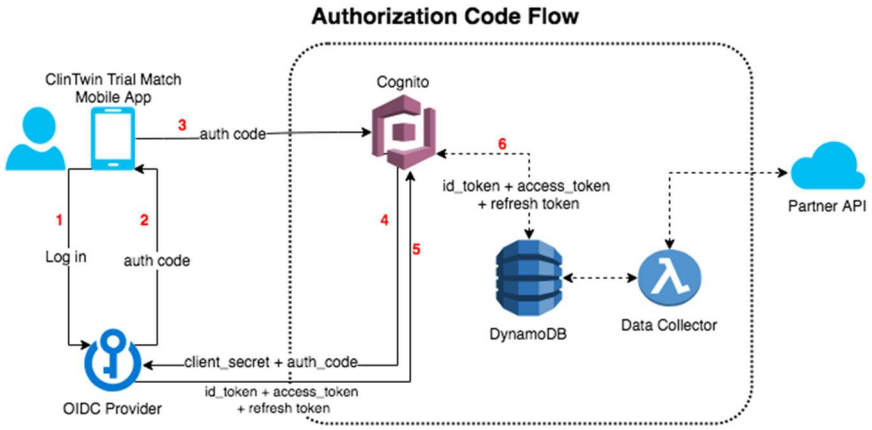
The simplicity of the data model makes the incoming data stream idempotent, allowing the collection efforts to be parallelized. If there is processing failure at various points of the ingestion, data can be reprocessed if necessary. There is an at-least-once processing guarantee on the data, and data ordering is not an architecture constraint. By using this approach, ClinTwin360's throughput can scale over time as participants activate integrations. After the data has been collected and transformed, it is published to the message-driven PubSub system. This provides backpressure if data is being produced faster than backend consumers can process & persist it.



The concept of a digital twin centers around a single identity that is decorated by data provided by third-party integration partners. To model this identity, the managed solution AWS Cognito provides off-the shelf functionality for establishing a central end-user identity around which to center integration.[10] The *ClinTwin360* app can activate one or more identity options for participants like Facebook, Google, or enterprise SAML single sign-on options to establish an identity without a new set of credentials to manage.



Once a participant's identity is established, integrations can start being activated and associated to the identity (Flow 4 and 5). This provides context for the collector services to schedule and fetch data on behalf of participants. For this type of interaction, the industry standard authorization grant mechanisms have primarily standardized around IETF RFC 6749, implemented by OAuth 2.0 (see Appendix: OAuth 2.0 Workflow for details), and extended by OpenID Connect which is the most common access granting technique based on the existing web APIs in the marketplace produced by health sensor data providers.[14]



Authorization Code Flow
1. Redirect to OIDC provider login - user provides credentials 2. OIDC provider responds with auth_code 3. *ClinTwin360 Trial Match* Mobile App sends auth_code to Cognito 4. Cognito issues request to OIDC provider using auth_code and *ClinTwin360*'s client-id secret 5. OIDC provider responds with id_token, access_token, and refresh token 6. Tokens are secured and persisted to DynamoDB for usage in partner integration collector micro-services

Each integration that uses bearer token based access keys, like Fitbit Activity API and OAuth 2.0 invoke APIs on behalf of a participant from within ClinTwin360's infrastructure. The keys are secured in a persistent key-value store that is mapped to the participant's identity [15, 16]. AWS DynamoDB is a viable solution due to its at-rest & in-transit encryption features along with role based access controls at the data-row granularity. Those key-pair rows in DynamoDB will then be iterated over in the system's job scheduler (AWS CloudWatch Rules), used as input into serverless data collector instances.

For some partner integrations like Fitbit Activity and Peloton, there is state management aspect required per-participant's integration collection. In Peloton's Cycle API for example, due to the structure of the API, each time the web API is hit, a start and end date parameter is passed.[12] Ideally only new activities are ingested for efficiency, so for this class of problem a strongly consistent distributed data-store like Apache Zookeeper can be utilized to persist collector data-state metadata across collectors. In the case of Peloton, the last collected end-time, would be the next execution start-time.

Another class of data integration collectors are push-based. For example, one of FitBit's APIs called "Subscriptions" pushes data periodically to an API endpoint that is preconfigured[11]. This allows *ClinTwin360* to stay current with participants' data without having to implement polling or scheduling. For APIs like this, the collector is fronted by an API gateway which spins up a new serverless instance to collect, process and publish the data.

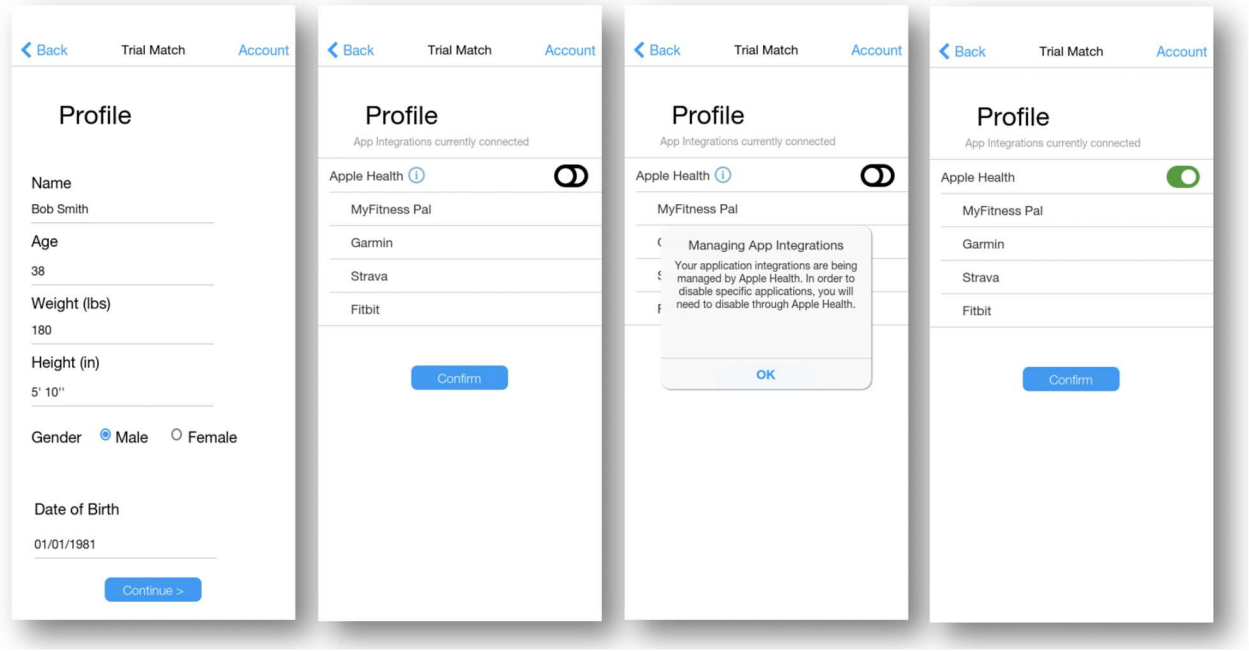
The last class of data integration collectors is on-device (Flow 6). Apple HealthKit API, for example, does not provide a web API for its data to be collected outside of Apple devices. Apple does however provide SDKs for apps running on participants' device to retrieve data.[13] This is where AWS AppSync comes into scope. AWS AppSync integrates with AWS Cognito so it ensures the participant's identity is associated with the data collected from the local device's HealthKit SDK calls.[10] AppSync buffers data collected locally to ease bandwidth usage on the participant's phone, as opposed to continuously streaming out the data. When enough data is buffered or an offline device reconnects, AWS AppSync syncs only the new updates since the last sync, not the entire local-storage. AppSync integrates with AWS Lambda functions, allowing the data collector instances to be built to transform and publish messages to Kinesis, similarly to the previous methods described.

Solution Demonstration

Trial Match - Participant App

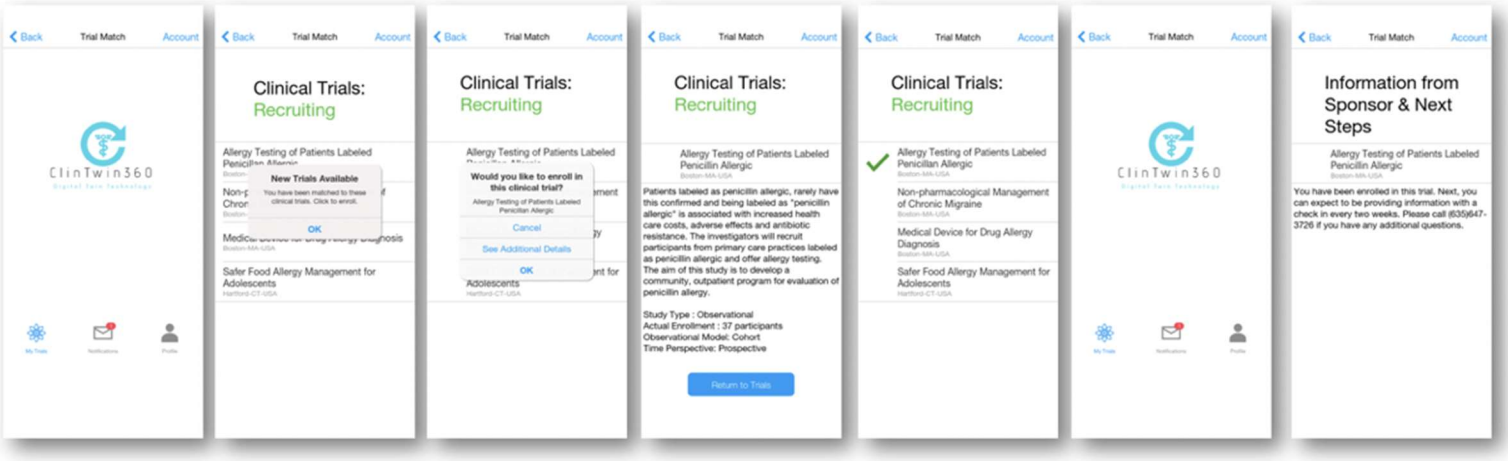
Profile Management

Trial Match users enter profile data as well as enable partner application integrations to enable their profile to be cross-matched to active trials to determine eligibility. [20]



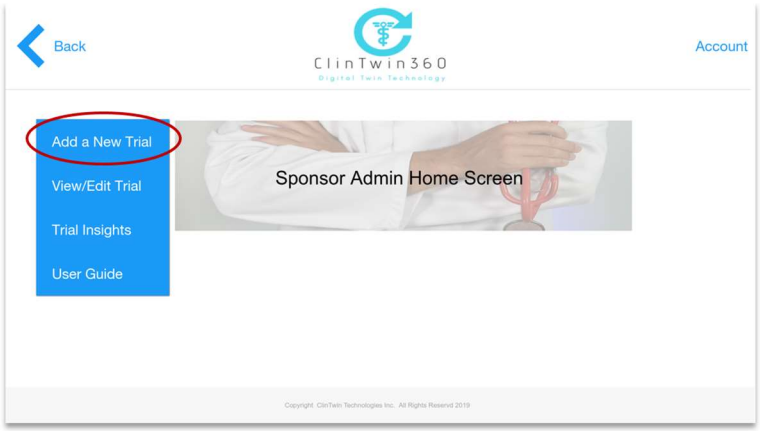
Clinical Trial Enrollment

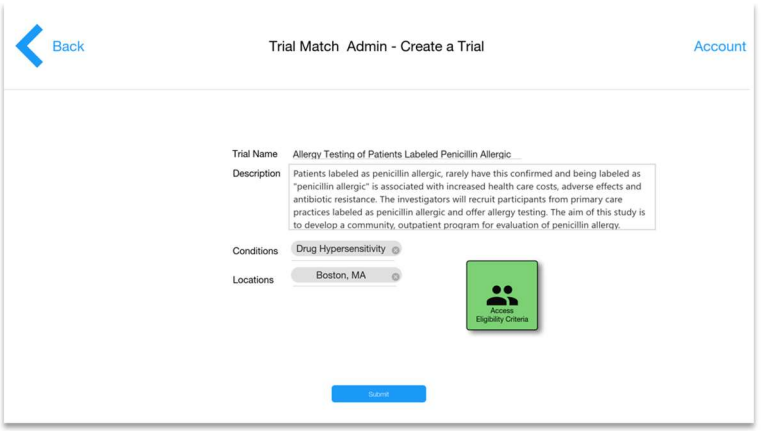
Trial Match users who are matched to active trials receive notifications of eligibility and can opt-in as trial participants.

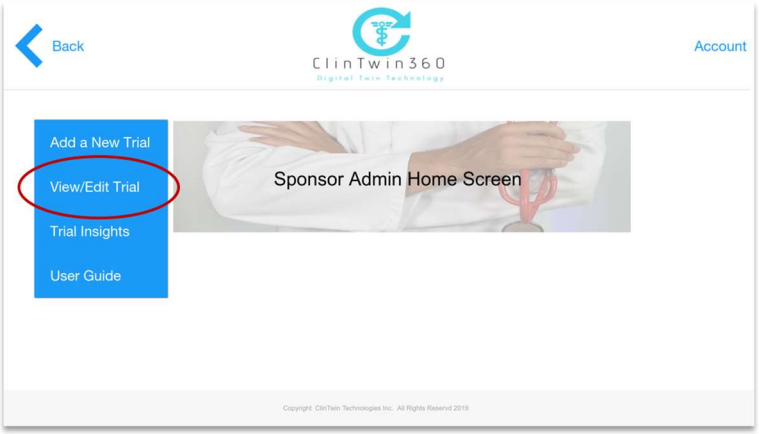


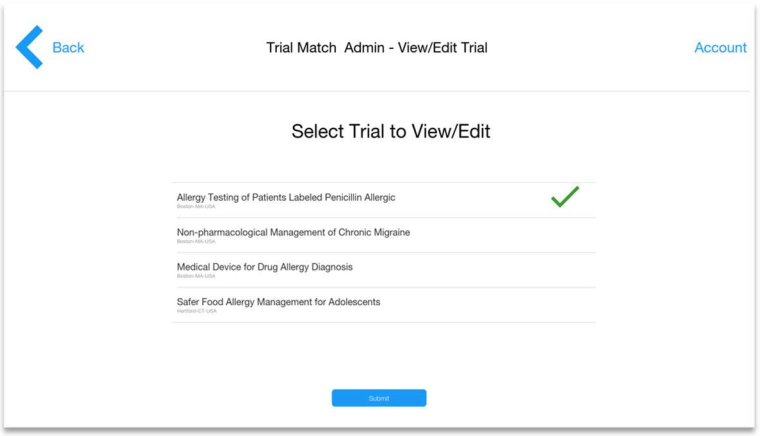
Trial Match - Sponsor Mobile App

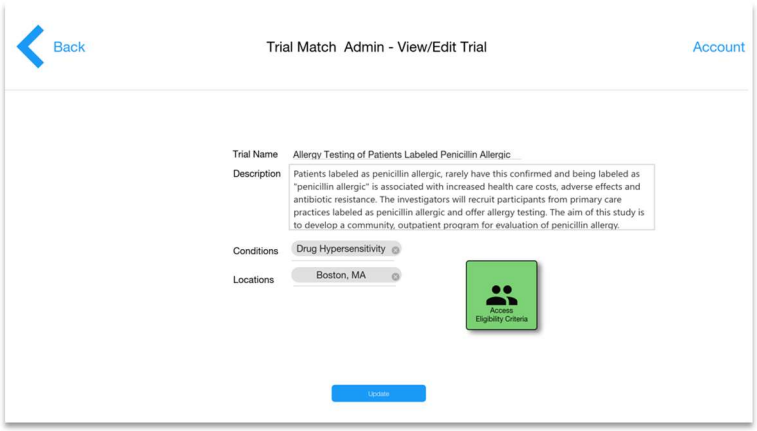
Trial Management

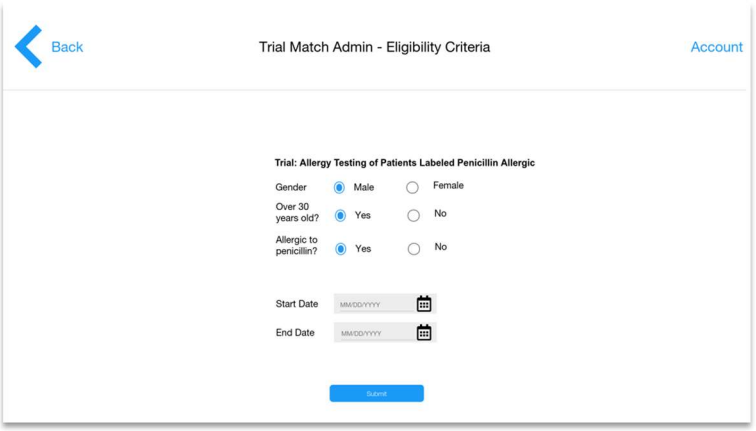










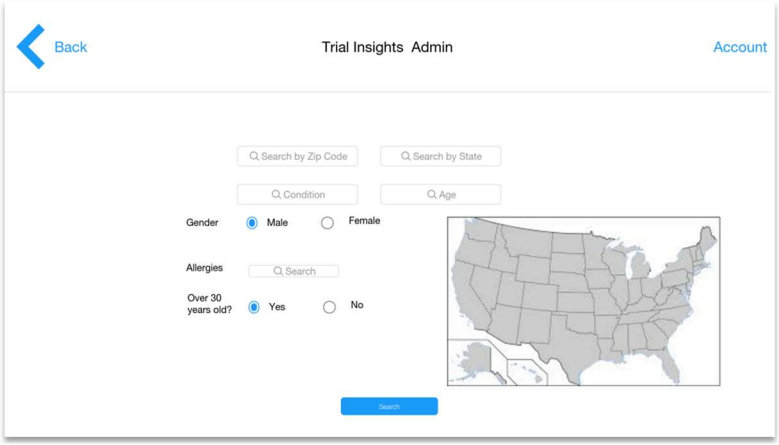


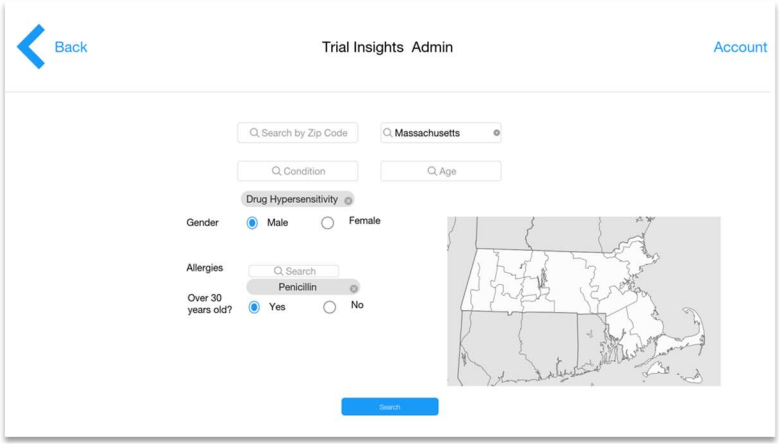
Trial Match enables sponsors to create a trial and manage enrollment eligibility criteria, which is used within the *Trial Match* Rules Engine to find eligible candidates within the *Trial Match* platform.

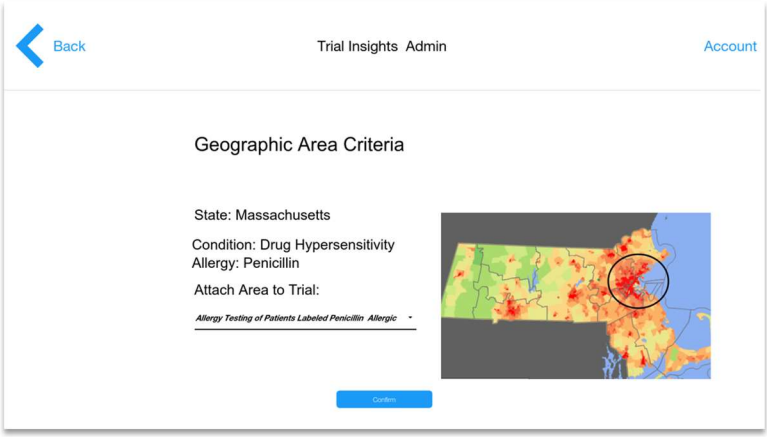
Trial Insights

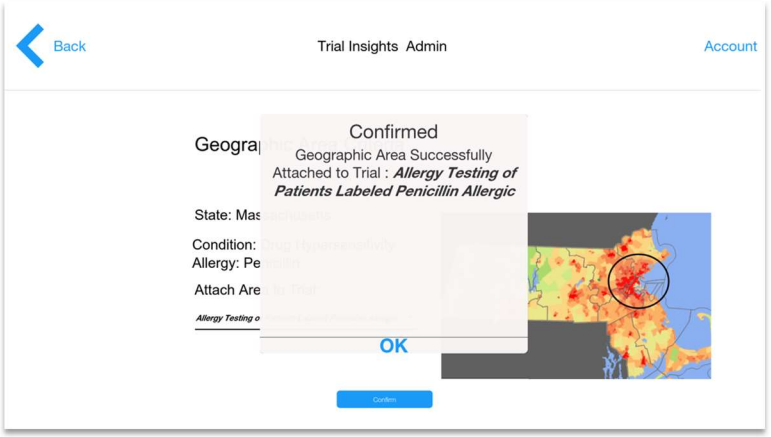
Hotspot Analysis

Trial Insights allows sponsors to analyze geographical hotspot data and link a specific region to a specific clinical trial that has interest in areas that show propensity to specific data values (e.g. areas where residents show hypersensitivity to drugs).



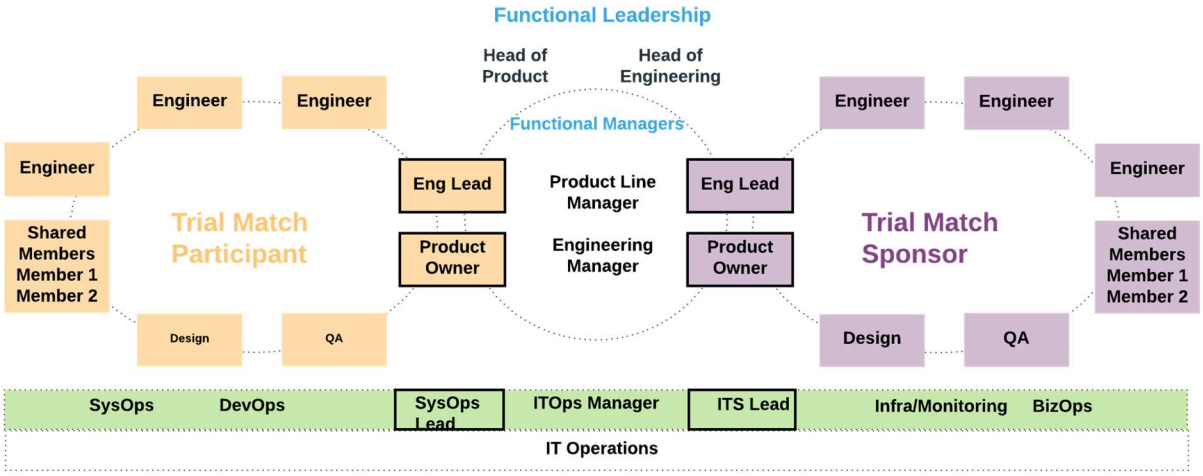






PART 3. IMPLEMENTATION PLAN

Solution Delivery Roadmap



The Solution Delivery Roadmap is organized into four distinct phases (Phase 1, Phase 2, Phase 3 and Future). Each phase provides specific product deliverables for key users (Participant, Sponsor, System Administrator). A product, a digital representation of a business component, aligns with a user role (Participant, Sponsor, System Administrator) and her journey on a platform or across platforms (*Trial Match*, *Digital Health Twin*, *Trial Insights*). Product teams create and operate their products on a platform. Product teams are cross-functional and comprised of Core, Shared and Supporting team members:

- Defined Core Members: Product Manager, 2-3 Engineers, UCD Design
- Assigned Shared Members: QA, UX, SRE
- Supporting Platform Team Members: SecOps, Tech/Ops, etc

Product teams are managed by Technology (Engineering Manager) and Business (Product Line Owner) managers who collaborate as peers and provide functional leadership across product teams within a specific platform. Shared resources work across platforms as needed for ongoing delivery and operations. The result is a “Product Universe” which continues to evolve with each phase deliverable.

Phase 1 | The Solution Delivery Roadmap for the *ClinTwin360* ecosystem is driven by time to market with minimized risk and technical complexity. To this end, the first solution delivery will be an MVP version of *Trial Match* that will focus on two core business capabilities: sponsor managed trial recruitment and trial matching using self-reported personal biometrics and general health related questions such as “Do you have a history of heart disease?”, “Are you Type 1 diabetic?”, “Do you use an inhaler?”. This will allow the solution to be delivered to the market quickly with minimal risk as there is no data integration requirements

for the MVP. The targeted business outcomes in this phase are to have contractual relationships with at least 5 sponsors and be managing 50 trials (0.2% market share) by the end of the phase.

<table>
<tr><td colspan="2">Phase 1
Key Deliverable | Trial Match MVP
Business Capabilities | Sponsor Managed Trial Recruitment and Self-Reported Data-Driven Trial Matching
Business Outcomes | 0.2% Trial Recruitment Market Share</td><td>Product Leadership
PLO - Trial Match
Eng Mgr - Trial Match</td><td>Shared Leadership
UCD Mgr
IT Ops Mgr</td></tr>
<tr><td colspan="2">Platform</td><td colspan="2">Product Team</td></tr>
<tr><td colspan="2">Platform | Trial Match
User Journey: Participant
Product: Participant Mobile App
Key Activities | Standing up dev, devint, integration, stage and production environments. Establishing team cadence. UI/UX for trial match workflow and informed consent.</td><td colspan="2">Trial Match Participant Mobile 1 PM 3 Full Stack iOS 1 Design</td></tr>
<tr><td colspan="2">Platform | Trial Match
User Journey | Sponsor
Product | Sponsor Web Portal
Key Activities | Standing up dev, devint, integration, stage and production environments. Establishing team cadence. UI/UX for trial management and eligibility criteria data entry.</td><td colspan="2">Trial Sponsor Application Team 1 PM 2 Full Stack Engineers 1 Design</td></tr>
<tr><td colspan="2">Platform | Trial Match
User Journey | System Administrator
Product | Admin Tools
Key Activities | Establishing data governance, security and roles to properly manage PII data.</td><td colspan="2">Platform and Permissions 1 PM 2 Full Stack Engineers 1 Infrastructure Architect</td></tr>
<tr><td colspan="4">Shared Resources | ITS (1), DevOps (3), QA (3) Design (1)</td></tr>
<tr><td colspan="2">Key Tasks and Milestones
Market Roll-Out of Trial Match MVP
Sponsor Managed Trial Recruitment
Sponsor entered eligibility criteria
Self-Reported Data
App enabled profile data capture
Trial Matching
Rules engine driven trial matching
Trial match notifications
Informed consent workflow</td><td colspan="2">Dependencies & Constraints
Sponsor engagement at target levels (5 sponsors)
Trial enablement of 50 trials
User engagement at target levels (dependent upon on-boarded trials)</td></tr>
</table>

Phase 2 | The second phase is focused on expanding trial matching beyond self-reported data by adding in device and app recorded biometric data collection. This opens the door to service recruitment for a much greater array of trials and takes the data capture out of the hands of the participant which allows for a higher volume of more accurate data. The targeted business outcomes in the second phase are to increase the

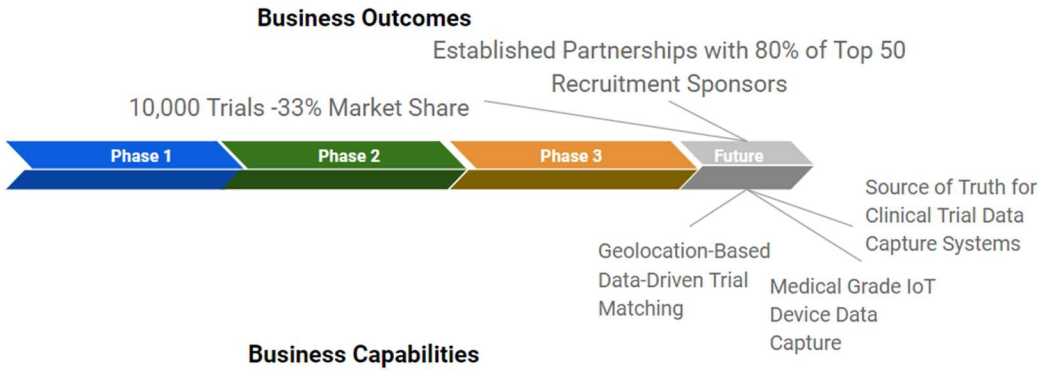
monthly on-boarding rate with at least 250 trials on-boarded (1% market share) and develop contractual relationships with at least 25 sponsors.

<table>
<tr><td colspan="2">Phase 2
Key Deliverable | Device and App-recorded biometric data collection
Business Capabilities | Biometric Data-Driven Trial Matching
Business Outcomes | 1% Trial Recruitment Market Share</td><td>Product Leadership
PLO - Trial Match
Eng Mgr - Trial Match</td><td>Shared Leadership
UCD Mgr
IT Ops Mgr
Data Mgr</td></tr>
<tr><td colspan="2">Platform</td><td colspan="2">Product Team</td></tr>
<tr><td colspan="2">Platform | Trial Match
User Journey | Participant
Product |Participant Mobile App
Key Activities | UI/UX for Apple Health data integration authorization.</td><td colspan="2">Trial Match Participant Mobile
● 1 PM
● 3 Full Stack iOS
● 1 Design</td></tr>
<tr><td colspan="2">Platform | Trial Match
User Journey | Sponsor
Product | Sponsor Web Portal
Key Activities | UI/UX for expanded eligibility criteria data entry.</td><td colspan="2">Trial Match Sponsor Web
● 1 PM
● 2 Full Stack Engineers
● 1 Design</td></tr>
<tr><td colspan="2">Platform | Digital Health Twin
User Journey | System Administrator
Product | Admin Tools
Key Activities | Establishing appropriate Apple Health integration cadences. Implementing and managing increased data storage/data lake solution, security and governance requirements.</td><td colspan="2">Data Integrations
● 1 PM
● 1 Integration Architect
● 2 Principal Data Engineers/Scientists
● 1 Big Data Engineer
● 2 API Engineers</td></tr>
<tr><td colspan="4">Shared Resources | ITS (1), DevOps (3), QA (3), Design (1)</td></tr>
<tr><td colspan="2">Key Tasks and Milestones
● Sponsor Managed Trial Recruitment with Expanded Biometric Data
○ Sponsor entered expanded eligibility criteria
● Biometric Data Capture
○ Data integration with Apple Health via ResearchKit SDK
○ Build out of digital health twin platform</td><td colspan="2">Dependencies & Constraints
● Sponsor engagement at target levels (25 sponsors)
● Trial enablement of 250 trials
● User engagement at target levels (dependent upon on-boarded trials)
● ResearchKit SDK Integration</td></tr>
</table>

Phase 3 | The third phase of the solution delivery is enabling the analytics platform. With Phase 2, the build out of each participant's digital health twin was initiated. By accumulating the digital health twin data over the duration of Phase 2 - Trial Insights now has the necessary volume of data to start delivering comprehensive analytics to the sponsors. The targeted business outcomes in the third phase are to increase the monthly on-boarding rate with at least 600 trials on-boarded (2% market share) and develop contractual relationships with at least 60 sponsors.

<table>
<tr><td colspan="2">Phase 3
Key Deliverable | Enabling the Trial Insights Analytics Platform
Business Capabilities | Trial Recruitment Analysis and Trial Recruitment Feedback Loop
Business Outcomes | 2% Trial Recruitment Market Share</td><td>Product Leadership
PLO - Trial Match
Eng Mgr - Trial Match</td><td>Shared Leadership
UCD Mgr
IT Ops Mgr
Data Mgr</td></tr>
<tr><td colspan="2">Platform</td><td colspan="2">Product Team</td></tr>
<tr><td colspan="2">Platform | Trial Insights
User Journey | Sponsor
Product | Analytics Application
Key Activities | Integrate a secure trial analytics solution within the sponsor web-portal.</td><td colspan="2">Trial Sponsor Application Team
● 1 PM
● 2 Full Stack Engineers
● 1 Design</td></tr>
<tr><td colspan="2">Platform | Digital Health Twin and Trial Insights
User Journey | Administrator
Product | Trial Insights
Key Activities | Architect a segmented big data solution to provide sponsor with raw and aggregated trial data for trial retrospectives and trial matching continuous improvement</td><td colspan="2">Data Integrations
● 1 PM
● 1 Integration Architect
● 2 Principal Data Engineers/Scientists
● 2 API Engineers</td></tr>
<tr><td colspan="4">Shared Resources: ITS and Compliance (2), DevOps (3), QA (6), Design (1)</td></tr>
<tr><td colspan="2">Key Tasks and Milestones:
● Market Roll-out of Trial Insights
● Trial Recruitment Feedback Loop
● Trial Recruitment Analysis</td><td colspan="2">Dependencies & Constraints:
● Sponsor engagement at target levels (60 sponsors)
● Trial enablement of 600 trials
● User engagement at target levels (dependent upon on-boarded trials</td></tr>
</table>

Future | The future state of the solution delivery - by continuing to add in data integrations - including geolocation based contextual data and data from medical grade IoT devices and enabling the integration to the trials' electronic data capture systems - allows the ClinTwin360 ecosystem to service every aspect of a clinical trial from recruitment through participation. The business outcomes in this phase focus on on-boarding 33% of each year's clinical trials for recruitment and having consistent engagement with 80% of the top 50 clinical trial sponsors. At this point we will have clearly demonstrated ourselves as the industry leader in clinical trial recruitment enablement.



Product teams will continue to be created and aligned based on the requirements of future initiatives. Established product teams will continue to progress and operate their products for ongoing user value.

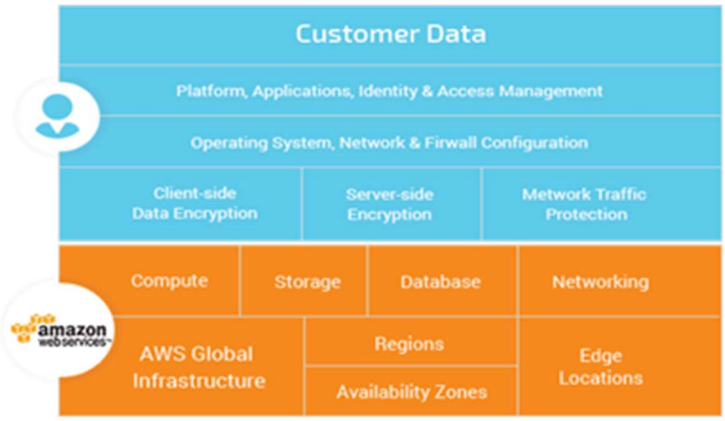
Operationalization

ClinTwin360's software is the primary touchpoint for customers - participants and sponsors. The functionality and user experiences directly correlate with the adoption and growth of the company. For this reason, solutions need to be well architected and instrumented with both functional and nonfunctional metric capabilities to proactively triage issues before they impact users. Agile teams are balanced, product-focused and user-centered.

Bugs and outages are a reality of enterprise IT, so having measurable, actionable alerts ensure that any components that fail are addressed quickly and contained a predetermined blast radius, and do not cause cascading failures that could bring down the entire system, corrupt data, or compromise security (see Appendix: Simple Operationalization Model for a summary).

Managed Services and Shared Responsibility

ClinTwin360 will leverage managed services where possible from Cloud providers like AWS, in order to focus efforts into delivering products & features, and get an MVP up and running quickly. As a new company, *ClinTwin360* will be able to scale infrastructural ure as it expands, and treat infrastructure costs as operational expenditure. Additionally, as a new company *with a new solution ecosystem, it is* not burdened by legacy, entrenched business operations and platforms, facilitating the operationalization effort. Finally, *ClinTwin360* is able to offload a portion of operations, security and compliance related to the physical infrastructure by relying on cloud-based service providers, mainly AWS through a defined Shared Responsibility Model.



Balanced Product Teams

Each Engineering team is organized cross-functionally as part of a balanced product team within a platform. A “you build it, you run it” mantra ensures that teams are empowered not only build, but operate their systems in the production environment. Two teams span product teams and *ClinTwin360* solution platforms: Technology Operations (Helpdesk) and Security Operations teams. These team members are responsible for consistency and availability in their respective areas, across the organization.

DevOps

Engineering teams follow DevOps best practices. All infrastructure is to be immutable infrastructure-as-code, deployed via CI/CD tools in order to ensure that only planned, version-controlled changes reach production, allowing for consistent, repeatable releases, and easier roll-back & root cause analysis in the event of an issue. Standardization of a commoditized, fungible infrastructure supports resource immutability while facilitating consistent quantitative measuring and monitoring at scale. This approach to commoditized infrastructure and services aligns well with an enhanced financial operations through an integrated IT Chargeback model for cost accounting of IT costs to the specific cost-center.

Administration and Support Operations

Role/Group	Responsibility
Tech Operations HelpDesk	Triage incidents tickets, execute run-book, manage knowledge-base and incident management tools
Security Operations	Develop, implement & enforce security policies, protocols and procedures. Run drills and security audits to ensure
Engineering Oncall	A rotation consisting of a member from each product engineering team on standby, ready to be escalated to, in the event of an incident.

Key Non-Functional Operational Components

Component	Detail
Service Catalog	Centrally managed IT services, governance and compliance for deploying approved IT services
Knowledge Management	A collaborative tool for aggregating organizational learnings, create and share operational runbooks.
CI/CD Tooling	Tool for releasing, testing, auditing, and deploying changes through a well-defined pipeline.
AWS Operational Services*	**OpsWorks**: Managed service for automated, scheduled or event-driven control of workflows across test, compliance and security as well as full stack automation for config deployment and change orchestration of applications and programmable infrastructure at scale. **Cloudwatch + CloudTrail:** Systems monitoring, management and alert service for actionable insights based on operational data (logs/metrics/events) across resources. Integrated with downstream event escalation notification tooling. Log, governance and operational auditing to continuously monitor, and retain infrastructure activity. **Systems Manager:** Operational insights for secure resource and application management, detection and resolution at scale operational ***All AWS Operational Services Utilized are HIPAA Eligible to store, process and transmit PHI** HIPAA Eligible Service Reference
Cross-team Communication	**Slack, Email**

Incident Management

ClinTwin360 will follow industry best practices for incident management utilizing a ticket creation, escalation and resolution workflow. Incidents are reported to a helpdesk. *Trial Match* and *Trial Insights* apps allow issues to also be submitted directly in the app. A self help support portal (T0) is available for *Trial Match* participants with access to chat and email support for basic customer issues (T1). The Support portal also documents legal, performance and privacy policy information for compliance and regulatory purposes.

Through the web application for *Trial Match* and *Trial Insights*, sponsors have direct access to dedicated support for on-boarding and management support as well as incident submission. Sponsor SLAs define ongoing support levels related to response, resolution and access to support team resources. Dedicated T2 as well as priority escalation for advanced or critical issue and incident resolution is only available for sponsor-side support. Sponsors can review and track their ticket history through the web applications.

Security Operations

A centralized security group will be assembled to ensure industry best practices are being adhered to. This includes educating employees, being involved in each product's design & code-review, reviewing static-code analysis reports, running penetration tests, creating incident response plans and defining least-

privilege data access-controls & governance. The security operations team will have insights into monitoring and alerting systems to track incoming/outgoing data usage, API requests, and have the ability to revoke API keys, disable partner integrations, or suspend users from ClinTwin360's products. These changes will be applied in *ClinTwin360*'s CI/CD tools so that an audit trail is maintained. As part of this team's data governance responsibilities, it will define role-based access policies in AWS IAM, defining the granularity of a sponsor's Trial Insights retrieval capabilities. This may include row-level DynamoDB policies, S3 Bucket policies, Lake Formation table and column policies, and defining post-processing data filters.

System Monitoring, Performance and Alerts

The following top-line metrics help indicate the overall health of the business. These are themes that directly or indirectly tie back to all metrics and monitoring systems implemented across products.

- ***Trial Match*:** Participants signups, daily active users, and number of quality trial matches
- ***Digital Health Twin*:** Integration partner data-points collected, proportional to the number of active integrations.
- ***Trial Insights*:** Daily active users, number of sponsor data-access requests fulfilled (queries, reports, job executions)

These top-line metrics show trends over time, which is not ideal for proactive, preventative action & resolution. *ClinTwin360* will invest in best in-class monitoring tools, making use of APM, centralized logging, and expect that these will evolve as engineering teams grow and identify needs over time. This will include SaaS tools like CloudWatch, Datadog, NewRelic, Prometheus and/or Kibana

Metrics will be exposed and continuously monitored over time. Anomaly alerts will be configured, and page operations teams, since usage patterns for each product are relatively predictable and can be an indicator of something going wrong in the environment. These metric trends will be reviewed quarterly by product owner teams who can use the metadata to focus engineering efforts in the most important areas. Metrics will also be used to feedback into the system to auto-heal and auto-scale.

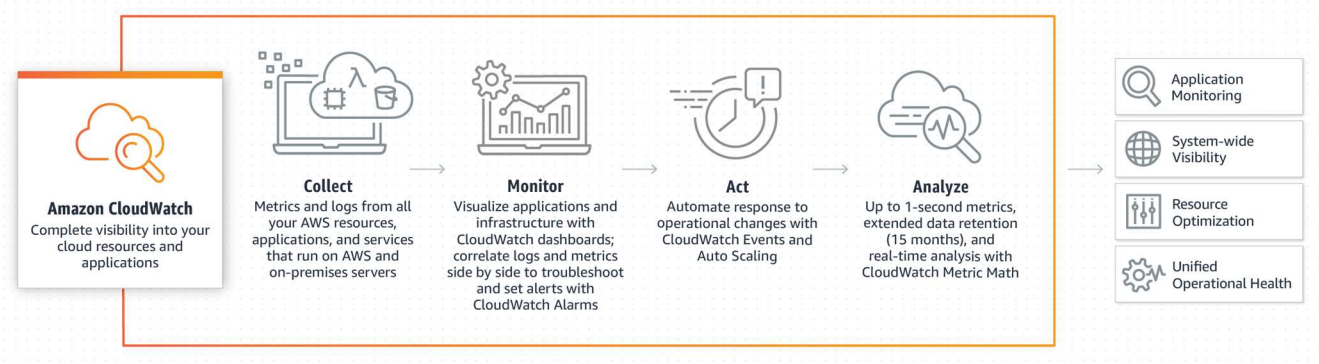
ClinTwin360's product suite will be instrumented with distributed tracing - Zipkin or NewRelic. By doing this, data workflows can be validated and throughput can be measured. Each piece of data that enters the system can be traced through each microservice and persistence layer with a unique trace-id that can explain why and how data originated (or lack thereof).

If product SLA thresholds are breached, an executive sponsor will be alerted and the recommended next-step will be to email our Trial Sponsors, keeping an open communication dialog through a well-defined incident notification procedure, documented in *ClinTwin360*'s knowledge management system. The messaging would include a summary of impact to their workload(s), actions being taken to resolve, and any estimates on when the issue would be resolved.

Lastly, access logs will be maintained in an aggregated system - CloudWatch. If an AWS IAM policy or system level access-controls are rejected based on lack of permissions, the security team will be alerted and perform after-action review.

Standard system metrics for health, resource performance and event-driven alerts and notifications can be found in the Appendix.

***ClinTwin360* Status** | A public facing status page displays platform performance and availability. A public status page illustrates ongoing performance of key systems and integrated 3rd party components. Real time status and performance is provided by AWS Cloudwatch system monitoring. Triggered alerts based on defined performance thresholds are delivered to support and technology staff using AWS SNS and managed based on defined escalation rules.



Source: https://aws.amazon.com/cloudwatch/

SLAs

SLA	Detail
Data-loss protection	99.999999999% data durability (via S3 and event sourcing architecture)
Redundant service availability	99.99% availability, providing data-center fail-over processing if availability zone or region is offline. “Blue-green” deployments ensure availability during rollouts.
App Responsiveness	All app requests to *Trial Match* must be served within 500ms
Insights Data Retrieval	• **“Warm”** Existing visualizations: 1 second • **“Cold”** New visualizations: 5 seconds • **“Ad-hoc”** MapReduce / Batch: 24 hours
New trial creation	All trials must be available within 1 minute of a sponsor’s creation
Ingestion Reliability	Partner integration data is made available to Digital Twin and Trial Insights within 5 minutes of

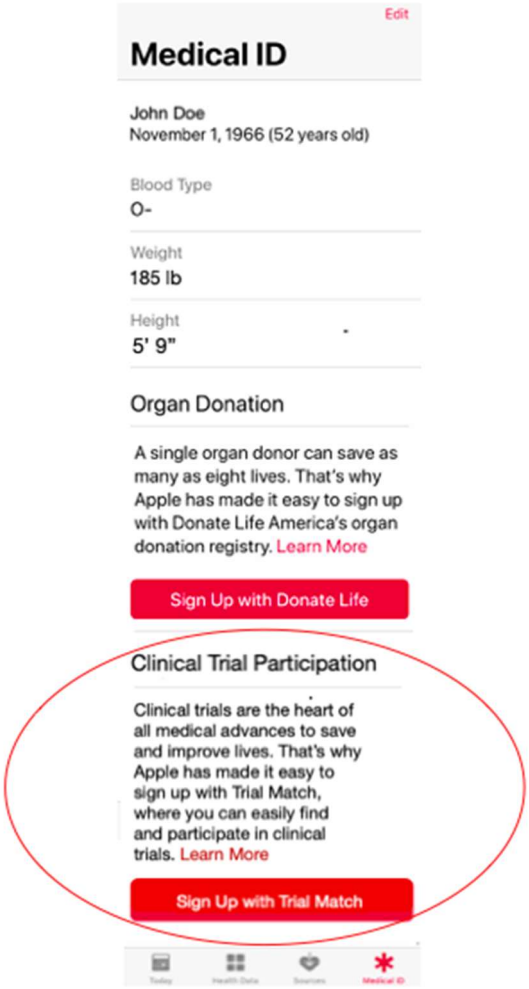
	being exposed in the partners API.
Support	Reporter is contacted within 3 hours of reporting an issue

Note: Response time estimates are based on a 95th percentile distribution to adjust for scaling, cache warming, cold-start, etc

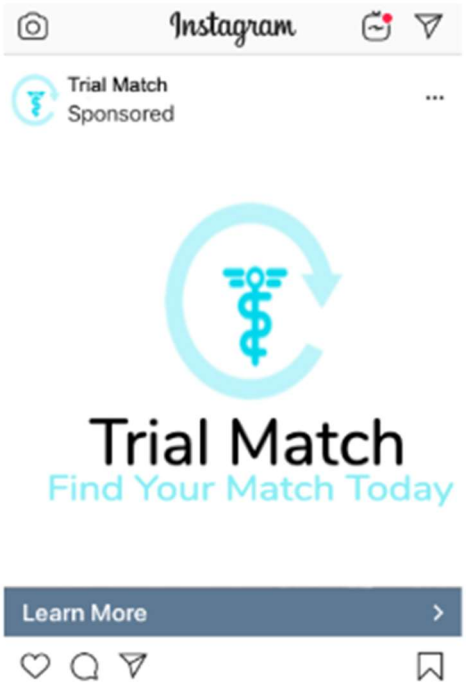
User Enablement

Participant Engagement

The MVP mobile app will utilize social media app advertisements and the Apple Health app to drive user engagement. The ads will target the specific demographics required by the active recruiting trials, as well as, utilize a 'do good' marketing approach to encourage individuals to register because volunteering for clinical trials is the 'right thing to do'. A call to action within the Apple Health app (pending approval from Apple) to proactively register will also drive user engagement.



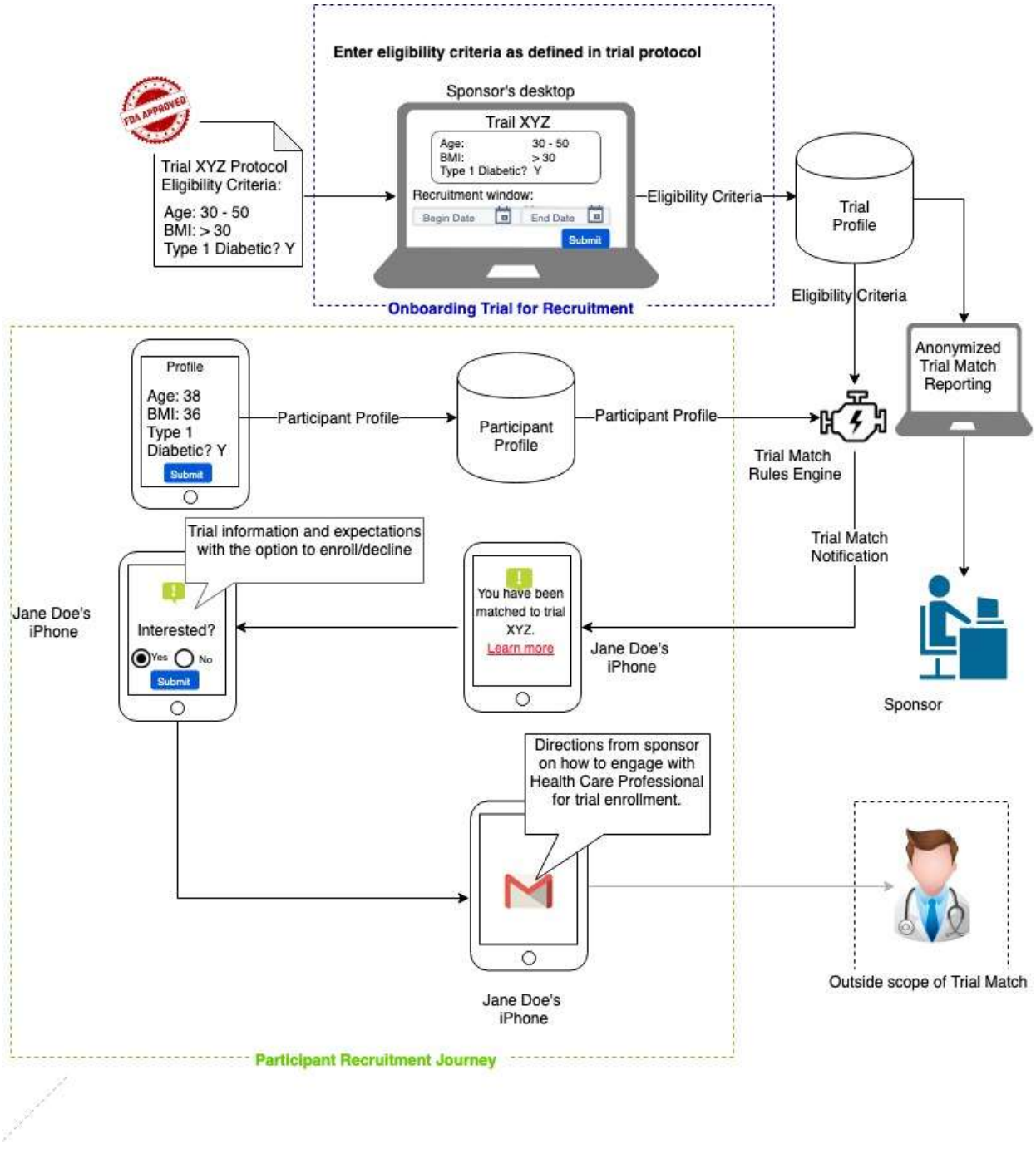
Sponsor Engagement

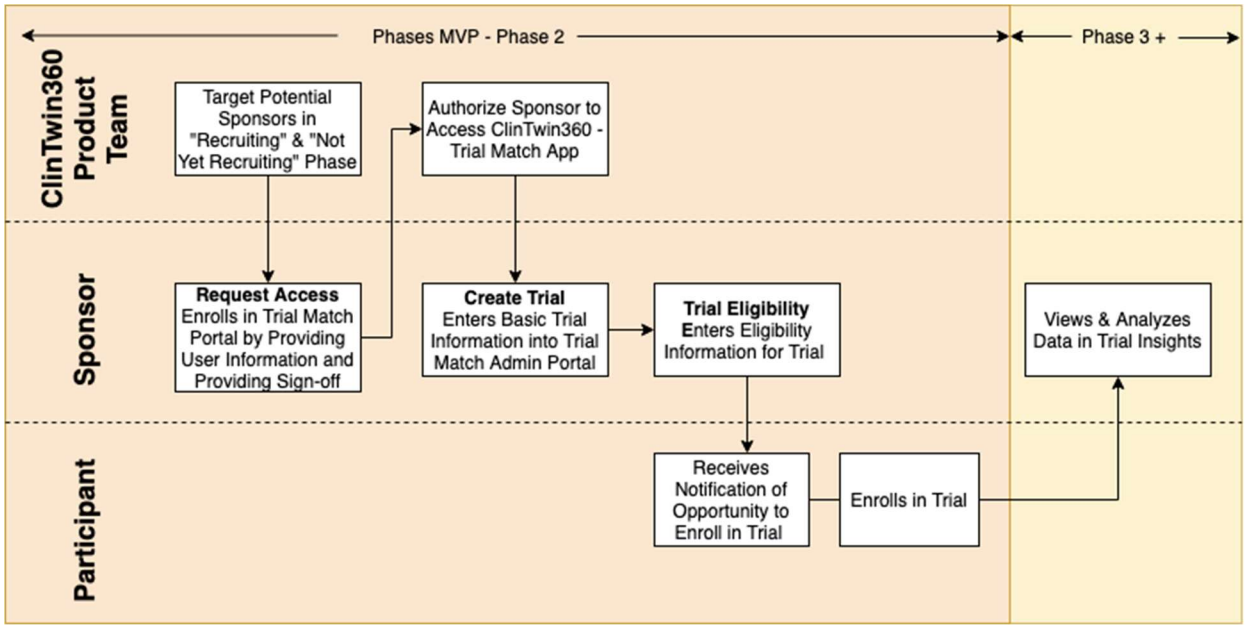


In order to on-board sponsors, clinical trial registration sites such as ClinicalTrials.gov will be utilized to source trials "not yet recruiting" and "recruiting" to target sponsors for conversion to *Trial Match* for recruitment.

User Journey

The following diagram depicts the sponsor's journey for on-boarding a trial in *Trial Match* for recruitment, as well as the participant's journey for engaging with *Trial Match* to be matched with a clinical trial.





Product Roll-out

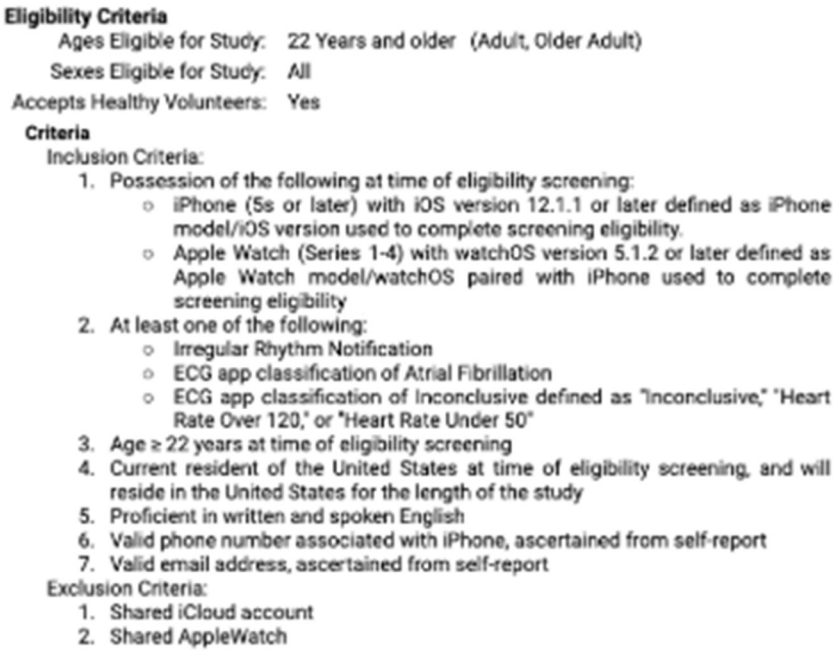
The products within the *ClinTwin360* ecosystem will be rolled out in a phased approach.

Phase 1 | The first product released within the *ClinTwin360* ecosystem will be a minimally viable product (MVP) version of the *Trial Match* application (mobile app and admin web portal) - targeting a 6 month development cycle. The MVP will focus on non-medical (i.e. behavioral, educational and social) clinical trials that can be matched to participants via basic information such as demographics, family profile (e.g. marital status, children, elderly parents), and standard health questions (e.g. diabetic, heart disease, obesity, etc.) self-reported within the user's *Trial Match* profile. These trials will not require matching data from any additional 3rd party data sources, and thus, will eliminate the need for data integrations which will minimize the complexity and risk of the initial roll-out.

Sponsor admins will manage the trials and their matching criteria within the *Trial Match* admin web portal. The participants will be identified as a match within *Trial Match*, however, all enrollment and trial participation will be administered under the control of the sponsors outside the scope of the *Trial Match* app. This phase will last approximately 9 months to one year. In this phase, 5-10 trials per month will be targeted for on-boarding.

Phase 2 | The second phase will expand into trial matching for medical and device trials with the ability for more sophisticated data matching and eligibility criteria. The more sophisticated data requirements will be met by using Apple's ResearchKit as it enables data collection from Apple Health which ingests data from not only users' Apple phones and watches but it also collects and aggregates data from any other applications the user has authorized. This eliminates the need for *ClinTwin360* to have to integrate individually with all of the thousands of integration compatible apps. The addition of the Apple Health

partner integration will enable expanding matching criteria to include data categories of activities, nutrition, sleep and mindfulness and well as expanded types of biometrics (See Apple Health Expanded Data Categories and Data Types for details).



Eligibility Criteria

Ages Eligible for Study: 22 Years and older (Adult, Older Adult)

Sexes Eligible for Study: All

Accepts Healthy Volunteers: Yes

Criteria

Inclusion Criteria:

1. Possession of the following at time of eligibility screening:
   - iPhone (5s or later) with iOS version 12.1.1 or later defined as iPhone model/iOS version used to complete screening eligibility.
   - Apple Watch (Series 1-4) with watchOS version 5.1.2 or later defined as Apple Watch model/watchOS paired with iPhone used to complete screening eligibility
2. At least one of the following:
   - Irregular Rhythm Notification
   - ECG app classification of Atrial Fibrillation
   - ECG app classification of Inconclusive defined as "Inconclusive," "Heart Rate Over 120," or "Heart Rate Under 50"
3. Age ≥ 22 years at time of eligibility screening
4. Current resident of the United States at time of eligibility screening, and will reside in the United States for the length of the study
5. Proficient in written and spoken English
6. Valid phone number associated with iPhone, ascertained from self-report
7. Valid email address, ascertained from self-report

Exclusion Criteria:

1. Shared iCloud account
2. Shared AppleWatch

Expanded Eligibility Criteria

This phase will last approximately one year with a goal of on-boarding 20-30 medical and non-medical trials per month.

Phase 3 | The third phase will involve the roll-out of the *Trial Insights* sponsor admin analytical portal that will take advantage of the Apple Health data collection enabled by Apple's ResearchKit SDK. This phase is estimated to last one year with the focus of hardening the clinical trial matching process, continuous enhancement of analytical capabilities and continued on-boarding of 30-50 trials per month.

Future Phases | Phases beyond the third phase will be targeted based on market and user demands with the following possibilities:

- Geolocation based partner application integration (e.g. environmental, socio-economic, commute, etc.)
- Medical grade device integrations
- ClinTwin360 clinical trial applications
- Clinical trial electronic data capture integrations

User Roles

There are three primary user roles within the *ClinTwin360* ecosystem:

- **System Administrator** | responsible for the health of the ecosystem.
- **Sponsor** | responsible for trial management within *Trial Match* and performing analytical analysis within *Trial Insights*.
- **Participant** | responsible for managing their *Trial Match* profile

Role	Privileges
System Administrator	All appropriate system privileges
Sponsor	***Trial Match*** ● Manage clinical trials including eligibility requirements ● Manage participants including accepting and withdrawing enrollments ***Trial Insights*** ● Perform trial retrospectives and analytical analysis ● Feed data recommendations back through to trials for continuous improvement
Participant	***Trial Match*** ● Manage user profile including authorization of partner application integration with Apple Health ● Data entry for trial matching ● Manage trial enrollment including user consent and data entry requirements ● Manage notifications and tasks related to enrolled clinical trials

Success Metrics

Phase 1

- Launch *Trial Match* MVP (participant app and admin portal)
- Achieve an Apple Application Store average rating of 3 or higher for the *Trial Match* MVP participant application
- 50% of *Trial Match* users register and create a profile after download and 30% of *Trial Match* registered users are active 90 days after download
- Receive *Trial Match* admin portal survey feedback that the admin portal meets or exceeds expectations
- On-board 45 non-medical trials
- Recruit 100% required enrollment in at least 80% of the on-boarded trials' recruitment window
- Receive trial sponsor survey feedback that *Trial Match* meets or exceeds expectations for at least 60% of the trials that fully on-boarded participants in the trials' recruitment window

Phase 2

- Establish Apple Health data integration as the foundation of the Digital Health Twin platform
- On-board 250 non-medical and medical clinical trials
- 60% of Trial Match downloads create a profile after download and 40% of *Trial Match* registered users are active 90 days after download
- Recruit 100% required enrollment in at least 85% of the on-boarded trials' recruitment window
- Receive trial sponsor survey feedback that *Trial Match* meets or exceeds expectations for at least 75% of the trials that fully on-boarded participants in the trials' recruitment window

Phase 3

- Launch *Trial Insights* analytic portal
- Receive *Trial Insights* analytic portal survey feedback that the *Trial Insights* analytic portal meets or exceeds expectations for at least 60% of the subscribed *Trial Insights* analytic portal users
- On-board 600 non-medical and medical clinical trials
- 65% of *Trial Match* users register and create a profile after download and 45% of *Trial Match* registered users are active 90 days after download
- Recruit 100% required enrollment in at least 88% of the on-boarded trials' recruitment window
- Receive trial sponsor survey feedback that the Trial Match meets or exceeds expectations for at least 85% of the trials that fully on-boarded participants in the trials' recruitment window

Future

- Establish additional key integrations with:
  - Geolocation based partner applications (e.g. environmental, socio-economic, commute)
  - Medical grade devices
  - Clinical trial electronic data capture systems
- Become the leader in clinical trial recruitment

Projected Revenue

When the above success criteria are achieved for our products and scaled across the addressable market of clinical trials ClinTwin360 projects revenues of:

- Year One: $3,100,000
- Year Two: $7,830,000
- Year Three: $18,300,000
- Year Four: $35,950,000
- Year Five: $49,000,000

Additional details on project revenues and expenses can be found in the Appendix - Product Financial Benefits section.

Bibliography

Part One

1. "89% of trials meet enrollment, but timelines slip, half of ... - Squarespace." https://static1.squarespace.com/static/5a9eb0c8e2ccd1158288d8dc/t/5aa2c28fec212d492f36cc8a/1520616079359/Jan-Feb+2013+IR+summary.pdf. Accessed 3 Mar. 2019.

2. "Patients Recruitment Forecast in Clinical Trials - Cognizant." https://www.cognizant.com/whitepapers/patients-recruitment-forecast-in-clinical-trials-codex1382.pdf. Accessed 3 Mar. 2019.

3. "The Real Cost Of Clinical Trials - Praxis." 25 Jul. 2017, https://www.gopraxis.com/real-cost-clinical-trials/. Accessed 3 Mar. 2019.

4. English, Rebecca A., Yeonwoo Lebovitz, and Robert B. Giffin. Transforming clinical research in the United States : challenges and opportunities : workshop summary. Washington, D.C: National Academies Press, 2010. Print.

5. "Clinical Research IO gets $1.6M for digital clinical trial data collection ...." 11 Jan. 2017, https://www.mobihealthnews.com/content/clinical-research-io-gets-16m-digital-clinical-trial-data-collection-platform. Accessed 3 Mar. 2019.

6. Institute of Medicine (US) Forum on Drug Discovery, Development, and Translation. Transforming Clinical Research in the United States: Challenges and Opportunities: Workshop Summary. Washington (DC): National Academies Press (US); 2010.

7. "The State of Clinical Research in the United States: An ... - NCBI - NIH." https://www.ncbi.nlm.nih.gov/books/NBK50886/. Accessed 3 Mar. 2019.

8. "Estimation of clinical trial success rates and ...." 31 Jan. 2018, https://academic.oup.com/biostatistics/advance-article/doi/10.1093/biostatistics/kxx069/4817524. Accessed 3 Mar. 2019.

Part Two

9. “Handline Push Notifications - AWS Pinpoint - AWS.” *Amazon Web Services, Inc.*, https://docs.aws.amazon.com/pinpoint/latest/developerguide/integrate-push.html Accessed 1 Apr. 2019.

10. “Amazon Cognito.” *Amazon.Com*, 2019, docs.aws.amazon.com/cognito/latest/developerguide/what-is-amazon-cognito.htm. Accessed 27 Mar. 2019.

11. “Fitbit Development: Subscriptions.” *Fitbit.Com*, 2016, dev.fitbit.com/build/reference/web-api/subscriptions/. Accessed 22 Mar. 2019.

12. “Geudrik/Peloton-Api.” *GitHub*, 30 May 2018, github.com/geudrik/peloton-api/blob/master/API_DOCS.md. Accessed 2 Apr. 2019.

13. “HealthKit - Apple Developer.” *Apple.Com*, 2019, developer.apple.com/healthkit/. Accessed 3 Apr. 2019.

14. Kawasaki, Takahiko. “Diagrams of All The OpenID Connect Flows.” *Medium*, Medium, 30 Oct. 2017, http://www.medium.com/@darutk/diagrams-of-all-the- openid-connect-flows-6968e3990660 Accessed 22 Mar. 2019.

15. “OAuth vs. OpenID – What’s the Difference? | Gluu | Blog.” *Gluu.Org*, 24 June 2014, www.gluu.org/blog/oauth-vs-openid-whats-the-difference/. Accessed 2 Apr. 2019.

16. “Fitbit Development: Using OAuth 2.0.” *Fitbit.Com*, 2019, dev.fitbit.com/build/reference/web-api/oauth2/. Accessed 1 Apr. 2019.

17. Menon, Pradeep. “Demystifying Data Lake Architecture.” *Medium*, Medium, 6 July 2017, http://www.medium.com/@rpradeepmenon/demystifying -data-lake-architecture-30cf4ac8aa07. Accessed 26 Mar. 2019.

18. *“Breathtaking Big Data”*, 2019, http://www.47lining.com/wordpress/ wp-content/uploads/ 2016/03/ data_lake_reference_architecture.png Accessed 3 Apr. 2019.

19. Paauwe, Mark. “Data Lake Definition - Dragon1.” *Dragon1.Com*, 2017, http://www.dragon1.com/terms/data-lake-definition Accessed 2 Apr. 2019.

20. “Find Trials - ClinicalTrials.Gov.” *Clinicaltrials.Gov*, 2017, clinicaltrials.gov/ct2/search. Accessed 4 Apr. 2019.

21. "Serverless Tutorial: Deploying Backend with your Frontend - AWS ...." https://docs.aws.amazon.com/amplify/latest/userguide/deploy-backend.html. Accessed 6 Apr. 2019.

22. "iOS - AWS Amplify." https://aws-amplify.github.io/docs/ios/start. Accessed 6 Apr. 2019.

23. "AWS Lake Formation Features - Amazon.com." https://aws.amazon.com/lake-formation/features/. Accessed 6 Apr. 2019.

24. "Integrating Amazon Pinpoint With Your Application."https://docs.aws.amazon.com/pinpoint/latest/developerguide/integrate.html. Accessed 5 Apr. 2019.

25. "Using Amazon Pinpoint Analytics with Amazon Cognito User Pools."https://docs.aws.amazon.com/cognito/latest/developerguide/cognito-user-pools-pinpoint-integration.html. Accessed 5 Apr. 2019

26. "An algorithm for caching predictive models" https://medium.com/rubrikkgroup/an-algorithm-for-caching-predictive-models-4f85b8eb3ff3. Accessed 16 May. 2019

APPENDIX

Clinical Trials Glossary

Clinical Trial Phase

Depending upon the nature and goal of the clinical trial, it is categorized within one of the following phases:

Phase 1 - The focus in Phase 1 is on safety. This phase tests experimental drugs on a very small group of individuals. In this phase, the researchers are trying to determine any adverse effects of the drug. Additionally, the researchers develop a drug administration protocol determined to have the highest possible efficacy with the lowest possible side effects.

Phase 2 - The focus in Phase 2 is on efficacy. In this phase of the trial, the number of individuals recruited for the trial increases and can be anywhere from 100-300 people on average. This phase can last for several years testing the efficacy of the drug as well as monitoring any additional adverse effects.

Phase 3 - The focus in Phase 3 is on verifying efficacy and safety on different populations, dosages and/or drug combinations. This phase is done with a very large number of participants and can be on average anywhere from 1,000 - 3,000 people. Since the number of people greatly increases, the trial is usually able to determine the extent of adverse effects the drug may have. This is when the FDA will consider the results of the trial to determine if the drug will be approved.

Phase 4 - The focus in Phase 4 is on verifying efficacy and safety on a large population. This phase takes place once the FDA has approved the drug. The participants in the trials increases dramatically and the safety and efficacy continues to be monitored.

Clinical Trial Recruitment and Adherence

In order to initiate a trial, a sponsor is first responsible for finding the required number of volunteers to participate in the trial as specified within the trial protocol. Recruitment is generally done by identifying doctors who are qualified to conduct the trial and who, with high probability, also have a relationship with qualified potential trial participants. The participants must provide informed consent and sign off once they understand all aspects of the trial and any possible risks and the benefits they receive to participate. During the trial, they have a right to confidentiality and privacy; the right to request their data; the right to withdraw at any time; and the right to the best possible care.

Throughout the course of the trial, the participants must adhere to the prescribed trial protocol which may include administration of medication and/or wearing or using a medical device. Additionally, the participant is usually required to visit the trial doctor according to the protocol visit schedule so data as defined within the protocol (e.g. weight, blood pressure, mobility, etc.) can be collected and submitted to the researchers.

Data used within the research is constrained to that collected as part of the trial as prescribed by the trial protocol.

The trial must adhere to the protocol for the duration of the trial as prescribed within the approved protocol. Any non-adherence, such as lack of data certification or ability to maintain enrollment numbers, could be cause for trial termination. At the conclusion of the trial, the sponsor submits the research to the FDA for approval.

Clinical Trial Eligibility Criteria Example

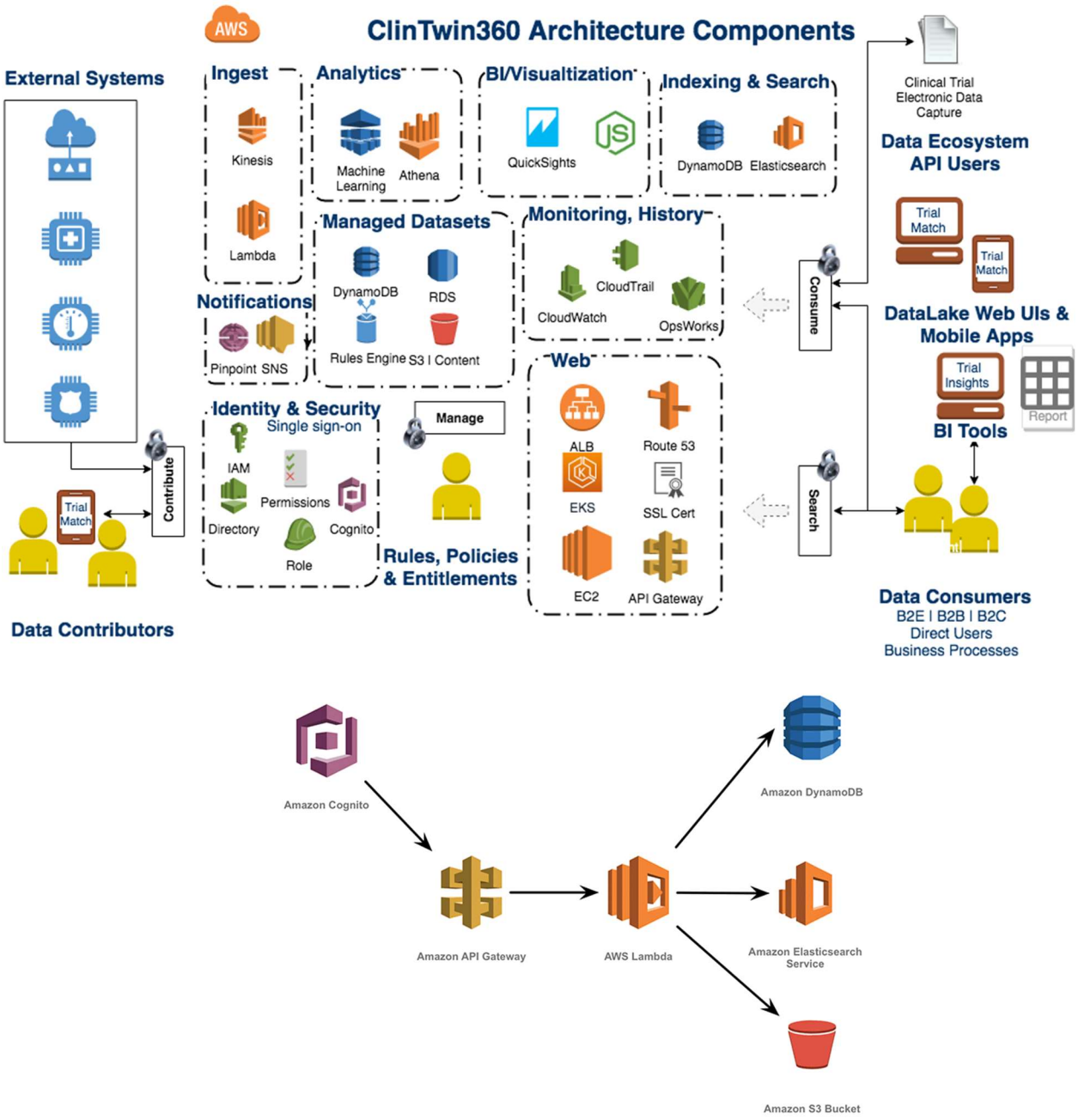
ELIGIBILITY CRITERIA

Inclusion Criteria	Comments (optional)	Yes	No
Example Only: Subject is at least 18 years of age	Date of Birth (DOB):		
Newly diagnosed with diabetes (within the last 6 months)	Date of Diagnosis:		
Prescribed oral medication for diabetes control	Name of Med/Dose:		
BP < 140/90 (screening visit)	Blood Pressure (BP):		

Exclusion Criteria	Comments (optional)	Yes	No
Subject has a history of: • myocardial infarction (MI) • coronary bypass graft (CABG)	Exclusion confirmed in:		
• abnormal liver function tests (LFT) (> 2 x upper limit of normal)	Date of LFT 1: Date of LFT 2:		
Pregnant or breastfeeding	Date of pregnancy test: Result: or LMP (last menstrual period)		
History of substance abuse (within the last 6 mos.)	Exclusion confirmed in:		

If any answers to inclusion criteria are 'no' or exclusion criteria 'yes', then participant is not eligible to be enrolled.

Data Lake Reference Architecture



https://aws.amazon.com/blogs/big-data/introducing-the-data-lake-solution-on-aws/

https://aws.amazon.com/quickstart/architecture/data-lake-foundation-with-zeppelin-and-rds/

Management | Control over user identity and security; rules, policies and entitlements governing the contribution, management, transformation and access of the data and monitoring of the data lake ecosystem.

Contribution | Ability to submit data from partner integrations and other external data for raw ingestion into the data management and orchestration pipeline for transformation into managed digital health twin datasets as well as published and analytical data.

Search | Ability to index and search the various current and historical digital health twin data contributions using facets, indices and views to return qualifying datasets in sub-second response times.

Consumption | Ability to consume the digital health twin data using the DataLake API into user-friendly web and mobile applications, BI visualization tools and also to data ecosystem API users.

Apple Health Expanded Data Categories and Data Types

Data Categories |

- **Activity** | contains information on how much you move. If only the iPhone hardware is used, this section contains information about steps, running and walking. Additional information is available with Apple Watch and additional partner applications.
- **Nutrition** | contains a breakdown self-reported diet data captured by partner applications.
- **Sleep** | details your sleeping habits which are enhanced with the use of partner applications and/or the Apple Watch.
- **Mindfulness** | details activity captured by partner applications while the participant is in a relaxed state.

In addition to the four main categories, Apple Health integration also enables matching on the following types of data:

- **Body Measurements** | self-reported body biometrics
- **Health Records** | CDA and health records as authorized by the user
- **Heart** | heart related measurements as reported by an external medical device, partner applications and/or Apple Watch
- **Reproductive Health** | reproductive health biometrics captured by partner applications.
- **Results** | various medical test results (e.g. sugar level insulin delivery, inhaler usage) captured by partner applications.
- **Vitals** | blood pressure, body temperature, heart rate, breathing rate as captured by partner applications and/or Apple Watch
- **Medical ID** | essential self-reported medical data (e.g. height, weight, age, blood type, emergency contacts, organ donation).

OAuth 2.0 Workflow

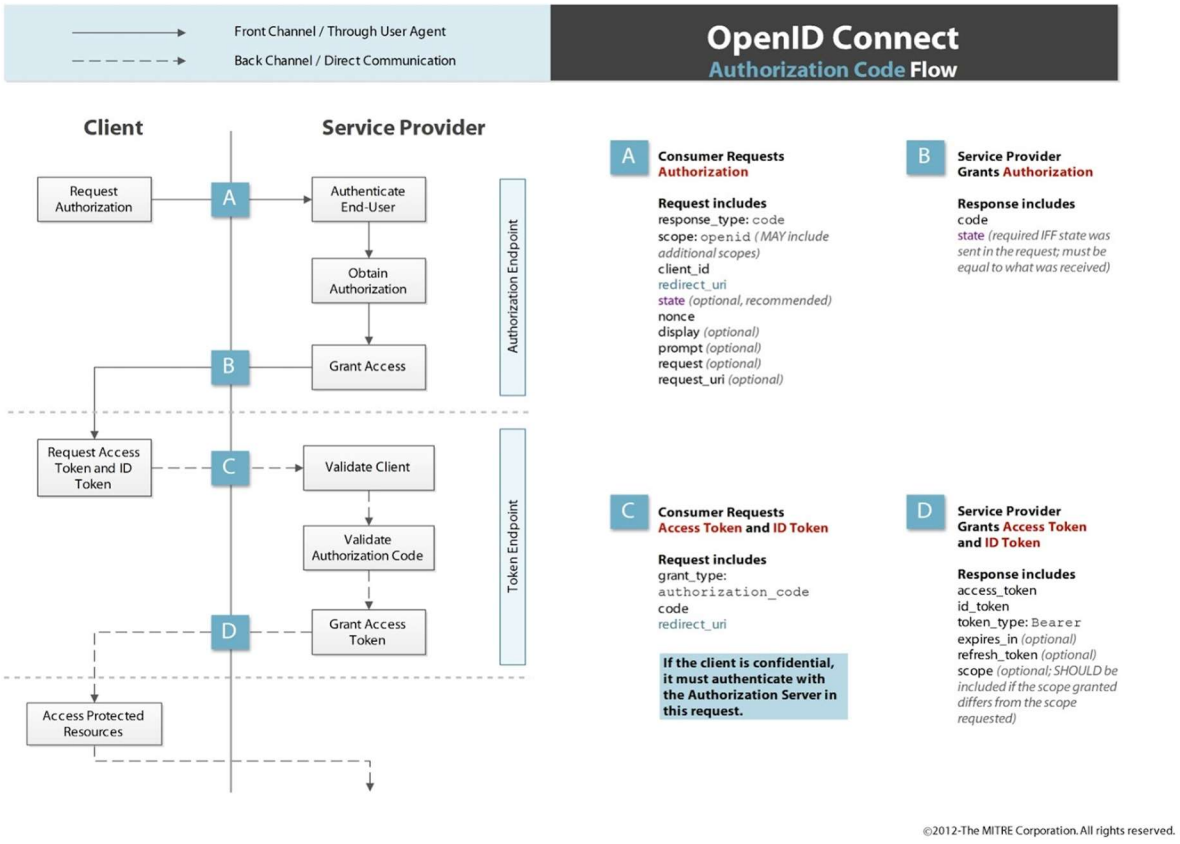


Figure Source: Kawasaki, Takahiko. “Diagrams of All The OpenID Connect Flows.”[14]

Partner Application Integration Data Formats

GPS Exchange Format (GPX)

```
<?xml version="1.0" encoding="UTF-8" standalone="yes" ?>
<gpx version="1.1"
    creator="EMTAC BTGPS Trine II DataLog Dump 1.0 - http://www.ayeltd.biz"
    xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance"
    xmlns="http://www.topografix.com/GPX/1/1"
    xsi:schemaLocation="http://www.topografix.com/GPX/1/1 http://www.topografix.com/GPX/1/1/gpx.xsd">
<metadata>
<name>GPS Receiver track log</name>
<desc>Tallinn (car)</desc>
<author>
<name>Michael Collinson</name>
<email id="mikes" domain="ayeltd.biz" />
<link href="http://www.ayeltd.biz"><text>AYE Ltd.</text></link>
</author>
<time>2007-10-02T09:22:06Z</time>
<keywords>Estonia, Tallinn, A. Weizbergi</keywords>
<bounds minlat="59.4367664166667" maxlat="59.4440920666666" minlon="24.74394385" maxlon="24.7971432"/>
</metadata>
<trk>
<src>Logged by Michael Collinson using EMTAC BTGPS Trine II</src>
<link href="http://www.ayeltd.biz"><text>AYE Ltd.</text></link>
<trkseg>
    <trkpt lat="59.4408327" lon="24.74516185">
        <ele>44</ele>
        <time>2007-10-02T07:54:30Z</time>
        <fix>3d</fix>
        <hdop>300</hdop><vdop>300</vdop><pdop>300</pdop>
    </trkpt>
</trkseg>
</trk>
</gpx>
```

CDISC Operational Data Model (ODM)

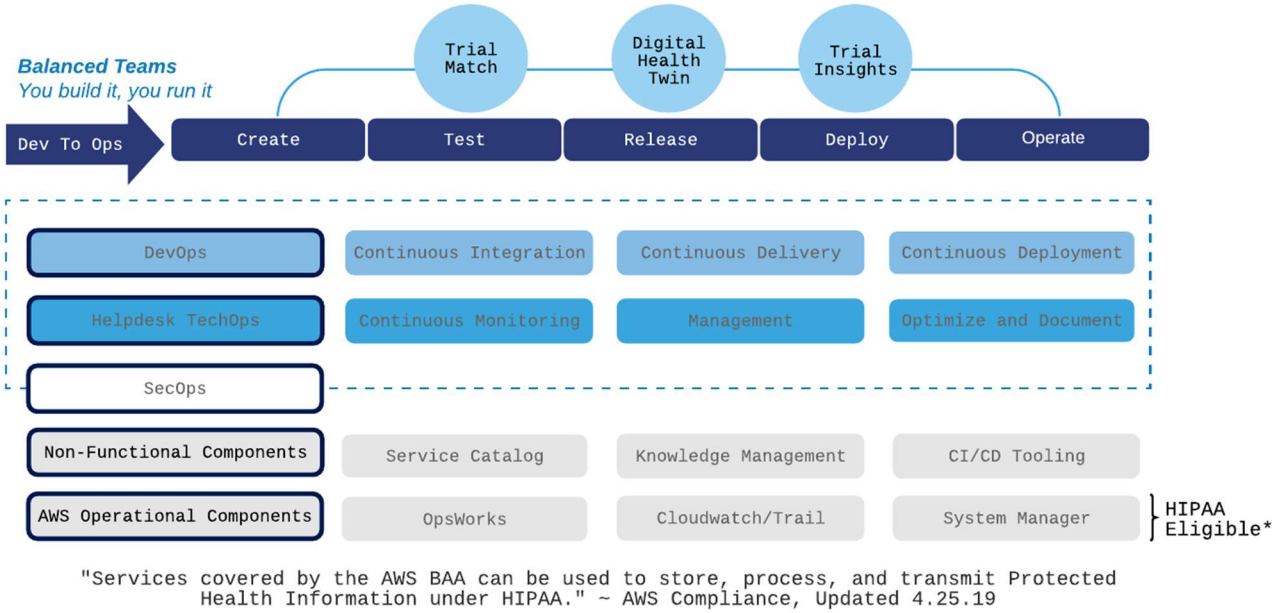
The CDISC Operational Data Model (ODM) is designed to facilitate the regulatory-compliant acquisition, archive and interchange of metadata and data for clinical research studies.

```
      ItemGroupData element for the Demographics part of the form
    -->
  ▼<ItemGroupData ItemGroupOID="DEMOG" ItemGroupRepeatKey="1">
    <ItemData ItemOID="PT" Value="P001"/>
    <ItemData ItemOID="INITIALS" Value="AMH"/>
    <ItemData ItemOID="SEX" Value="f"/>
    <ItemData ItemOID="DOB" Value="1947-07-16"/>
    <ItemData ItemOID="SPONSOR_PTID" Value="B00-2136-001"/>
    <ItemData ItemOID="WEIGHT_LB" Value="150"/>
    <ItemData ItemOID="WEIGHT_KG" Value="68.18"/>
   ▼<!--
        ItemGroupData element for the Vitals part of the form
    -->
  </ItemGroupData>
  ▼<ItemGroupData ItemGroupOID="VITALS" ItemGroupRepeatKey="">
    <ItemData ItemOID="PT" Value="P001"/>
    <ItemData ItemOID="VISITNAME" Value="Visit1"/>
    <ItemData ItemOID="SBP" Value="120"/>
    <ItemData ItemOID="DBP" Value="80"/>
    <ItemData ItemOID="SPONSOR_PTID" Value="B00-2136-001"/>
    <ItemData ItemOID="OCCUR_NUM" Value="1"/>
  </ItemGroupData>
</FormData>
```

Training Center XML

```
<?xml version="1.0" encoding="UTF-8"?>
<TrainingCenterDatabase
  xsi:schemaLocation="http://www.garmin.com/xmlschemas/TrainingCenterDatabase/v2 http:
  xmlns:ns5="http://www.garmin.com/xmlschemas/ActivityGoals/v1"
  xmlns:ns3="http://www.garmin.com/xmlschemas/ActivityExtension/v2"
  xmlns:ns2="http://www.garmin.com/xmlschemas/UserProfile/v2"
  xmlns="http://www.garmin.com/xmlschemas/TrainingCenterDatabase/v2"
  xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance" xmlns:ns4="http://www.garmin.c
  <Activities>
    <Activity Sport="Running">
      <Id>2015-01-20T13:26:30.000Z</Id>
      <Lap StartTime="2015-01-20T13:26:30.000Z">
        <TotalTimeSeconds>419.855</TotalTimeSeconds>
        <DistanceMeters>1000.0</DistanceMeters>
        <MaximumSpeed>2.8459999561309814</MaximumSpeed>
        <Calories>64</Calories>
        <Intensity>Active</Intensity>
        <TriggerMethod>Manual</TriggerMethod>
        <Track>
          <Trackpoint>
            <Time>2015-01-20T13:26:30.000Z</Time>
            <Position>
              <LatitudeDegrees>25.06334876641631</LatitudeDegrees>
              <LongitudeDegrees>121.6330941952765</LongitudeDegrees>
            </Position>
            <AltitudeMeters>19.799999237060547</AltitudeMeters>
            <DistanceMeters>0.0</DistanceMeters>
            <Extensions>
              <TPX xmlns="http://www.garmin.com/xmlschemas/ActivityExtension/v2">
                <Speed>0.0</Speed>
                <RunCadence>0</RunCadence>
              </TPX>
            </Extensions>
          </Trackpoint>
          <Trackpoint>
            <Time>2015-01-20T13:26:41.000Z</Time>
            <Position>
              <LatitudeDegrees>25.06322412751615</LatitudeDegrees>
              <LongitudeDegrees>121.63292722776532</LongitudeDegrees>
            </Position>
            <AltitudeMeters>19.0</AltitudeMeters>
            <DistanceMeters>21.8700008392334</DistanceMeters>
            <Extensions>
```

Simple Operationalization Model



"Services covered by the AWS BAA can be used to store, process, and transmit Protected Health Information under HIPAA." ~ AWS Compliance, Updated 4.25.19

Product Financial Benefits

A high level summary of each of *ClinTwin360's* product categories and estimated revenues and expenses by category for the first five years are provided in this section.

Projected costs associated with corporate staff (non-sales) and sales staff are provided in their own table as they are common across all product categories. Corporate staff (non-sales) operating expenses include *ClinTwin360's* leadership, legal, finance, HR, marketing, and administrative support staff's salary and benefits. Sales staff operating expenses include salaries, benefits, and commissions for field sales, inside sales, sales management.

Description	Year 1		Year 2		Year 3		Year 4		Year 5	
CapEx/OpEx	**CapEx**	**OpEx**	**CapEx**	**OpEx**	**CapEx**	**OpEx**	**CapEx**	**OpEx**	**CapEx**	**OpEx**
Corporate Staff (Non-Sales)		$850k		$2.2M		$4.5M		$6.8M		$8.5M
Sales Staff		$800k		$2M		$5M		$8M		$14M

ClinTwin360 utilizes cloud based hosting that allows *ClinTwin360* to keep the initial capital spend low. *ClinTwin360's* operating costs grows as clinical trial participants join the platform and their rich contextual data is gathered into their digital twins' profiles and the analysis of that data grows by trial sponsors. The more users *ClinTwin360* onboards the greater our value proposition to trial sponsors which enables *ClinTwin360* to quickly ramp up our revenue and grow the margin per user over time.

ClinTwin360's revenue will be displayed to show fees associated with on-boarding of clinical trial sponsors and subscription services. On-boarding costs include clinical trial sponsor requested changes and front-loaded administrative charges. Subscription services include costs that are per clinical trial per month, per enrolled qualified clinical trial participant per month, and per trail optimization portal user per month.

Trial Match

The National Institute of Medicine (US) research found that 27% of United States Clinical trials fail to enroll any subjects, 75% of clinical trials fail to enroll the target number of subjects, and 90% of all clinical trials worldwide fail to enroll participants within the target amount of time and must extend their enrollment period.[6]

Sponsors needing to cancel clinical trials due to lack of participants and/or extend the enrollment window past their predefined target enrollment period can be multi-million dollar problems on each clinical trial. For a large trial, the clinical trial enrollment problem can be measured in the hundreds of millions to billions of dollars.

Revenue

Description	Year 1	Year 2	Year 3	Year 4	Year 5
Onboarding	$450k	$980k	$1.9M	$1.2M	$1.2M
Subscription	$900k	$2.1M	$5.2M	$10.4M	$16.6M

Expenses

Description	Year 1		Year 2		Year 3		Year 4		Year 5	
CapEx/OpEx	**CapEx**	**OpEx**	**CapEx**	**OpEx**	**CapEx**	**OpEx**	**CapEx**	**OpEx**	**CapEx**	**OpEx**
Developer Costs	$700k									
Cloud Hosting		$400k		$800k		$1.6 M		$3.20 M		$7.5 M
Marketing		$1.1 M		$600k		$500k		$400k		$300k

Digital Health Twin

An MIT study[8] published in the Journal of Biostatistics in 2018 found that 14% of all drugs in clinical trials eventually win approval from the FDA. In other words, the current state of clinical trials has an 86% failure rate.

In 2016 the Tuft Center for the Study of Drug Development estimated the cost of bringing a drug to market in the United States averaged $2.6 billion. Of the $2.6 billion in cost, Tufts estimated the average out-of-

pocket cost for a trial sponsor was $1.395 billion and $1.163 billion of time costs (expected returns that investors forgot while a drug is in development).

By providing rich contextual data *ClinTwin360* enables trial sponsors the opportunity to find insights through the contextual data (biometric sensor data, weather, air pollution, etc.) to fail fast by stopping drug development in phase one or phase two before incurring the time and cost of a phase three or phase four trial. Similarly, rich contextual data can enable sponsors to pivot to use the drug compound or therapeutic procedure from the clinical trial for a different purpose.

Even a 1% increase in clinical trial success from rich contextual data can yield a single sponsor an estimated savings of $26 million on average (1% of the $2.6b average clinical trial cost).

Revenue

Description	Year 1	Year 2	Year 3	Year 4	Year 5
Onboarding	$450k	$980k	$1.9M	$1.2M	$1.2M
Subscription	$900k	$2.8M	$5.9M	$14.4M	$18.6M

Expenses

Description	Year 1		Year 2		Year 3		Year 4		Year 5	
CapEx/OpEx	**CapEx**	**OpEx**	**CapEx**	**OpEx**	**CapEx**	**OpEx**	**CapEx**	**OpEx**	**CapEx**	**OpEx**
Developer Costs	$2.5 M									
Cloud Hosting		$400k		$800k		$1.6 M		$3.20 M		$7.5 M

Trial Insights

The analytic capability with a unified platform of contextual data that enables a trial sponsor's data scientists to determine enhancements to clinical trial protocols can further reduce a subscribing sponsor's clinical trial

failure rate. Being able to launch new clinical trials with better questions in the established clinical trial protocol can save a sponsor tens to hundreds of millions of dollars per future clinical trial.

Revenue

Description	Year 1	Year 2	Year 3	Year 4	Year 5
Onboarding	$50k	$120k	$500k	$650k	$900k
Subscription	$350k	$850k	$2.9M	$8.1M	$10.5M

Expenses

Description	Year 1		Year 2		Year 3		Year 4		Year 5	
CapEx/OpEx	**CapEx**	**OpEx**	**CapEx**	**OpEx**	**CapEx**	**OpEx**	**CapEx**	**OpEx**	**CapEx**	**OpEx**
Developer Costs	$2.5 M									
Cloud Hosting		$400k		$800k		$1.6 M		$3.20 M		$7.5 M

System Metrics

Standard system metrics for health, resource performance and event-driven alerts and notifications

Health	Resource-Specific	Events
Performance Throughput Success Error	Availability Utilization Saturation Error	Scale-related Code and Config

Standard Compute/DB Health Metrics
Performance: % or Duration Response Time **Throughput**: Requests/Queries Per Second **Success/Erro**r: % or Count of 2XX/5XX responses or queries leading to success or exceptions
Resource-Related Metrics
Availability: % or Duration for a resource to respond to requests. **Utilization**: The percentage or duration of time that the resource is busy or the resource's in-use capacity **Saturation**: Requested work that cannot be serviced, in queue

Specific examples of relevant system metrics include:

API Gateway Metrics CacheHitCount, CacheMissCount, Count, Latency
Cache Hit Count OR Cache Miss Count (CacheHit(Miss)Count): The number of requests served (or missed) from the API cache in a given period. ● The sum or average (hit rate) of the cache hits(misses) in the specified period. ● **Unit**: Count **Count (SampleCount):** Total number API requests in a given period. ● **Unit**: Count **Latency:** Time between when the API Gateway receives a client request and when it returns a response including the integration latency and overhead.

Unit: Millisecond

Amazon EMR (Elastic Map Reduce)
MapTasksRunning, MapTasksRemaining, MapSlotsOpen, RemainingMapTasksPerSlot, ReduceTasksRunning, ReduceTasksRemaining

Tasks Running (MapTasksRunning): Number of running map tasks for each job.

- Monitor cluster progress
- **Units**: Count

Tasks Remaining (MapTasksRemaining): Number of remaining map tasks for each job. A remaining map task is one that is not in any of the following states: Running, Killed, or Completed.

- Monitor cluster progress
- **Units**: Count

Capacity Available: (MapSlotsOpen) The unused map task capacity. This is calculated as the maximum number of map tasks for a given cluster, less the total number of map tasks currently running in that cluster.

- Analyze cluster performance
- **Units**: Count
- **RemainingMapTasksPerSlot:** Ratio of mapped to remaining slots available

Reduce Tasks Count (ReduceTasksRunning): The number of running reduce tasks for each job.

- Monitor cluster progress
- **Units**: Count
- **ReduceTasksRemaining:** The number of remaining reduce tasks for each job.

RDS and DB Performance Metrics (Redshift/EC2 as applicable)
DBLoad, DBLoadCPU, DBLoadNonCPU, IncomingBytes

Database Load (DBLoad): The number of active sessions for the DB engine. Average number of active sessions.

Database CPU Load (DBLoadCPU): The number of active sessions where the wait event type is CPU. This is filtered by the wait event type CPU.

Non Load
DBLoadNonCPU: The number of active sessions where the wait event type is not CPU.

Streaming Data (Kinesis)
IncomingBytes, IncomingRecords, Put Latency, Put Records, Throughput

IncomingBytes
The number of bytes successfully put to the Kinesis stream over the specified time period.

- This metric includes bytes from Put operations.
- Minimum, Maximum, and Average statistics represent the bytes
- **Statistics:** Minimum, Maximum, Average, Sum, Samples
- **Units:** Bytes

IncomingRecords
The number of records successfully put to the Kinesis stream over the specified time period.

- This metric includes record counts from PutRecord and PutRecords operations.
- Minimum, Maximum, and Average statistics for a single put operation for a stream in a specified period
- **Statistics:** Minimum, Maximum, Average, Sum, Samples
- **Units:** Count

Put Latency (PutRecord.Latency): The time taken per PutRecord operation, measured over the specified time period.

- **Statistics: Minimum, Maximum, Average**
- **Units: Milliseconds**

PutRecords.Records: The number of successful records in a PutRecords operation per Kinesis stream, measured over the specified time period.

- **Statistics:** Minimum, Maximum, Average, Sum, Samples
- **Units:** Count

Throughput (ReadProvisionedThroughputExceeded): Number of GetRecords calls throttled for the shard over time.

- **Exception counts for AWS dimensions:** 5 reads per shard per second or 2 MB per second per shard. The most commonly used statistic for this metric is Average.
- **Stream-level metric name:** ReadProvisionedThroughputExceeded
- **Statistics:** Minimum, Maximum, Average, Sum, Samples
- **Units:** Count