# CHANGING OUTLOOKS OF CLINICAL TRIAL OPERATIONS AND CLINICAL DATA MANAGEMENT WITH COVID PANDEMIC

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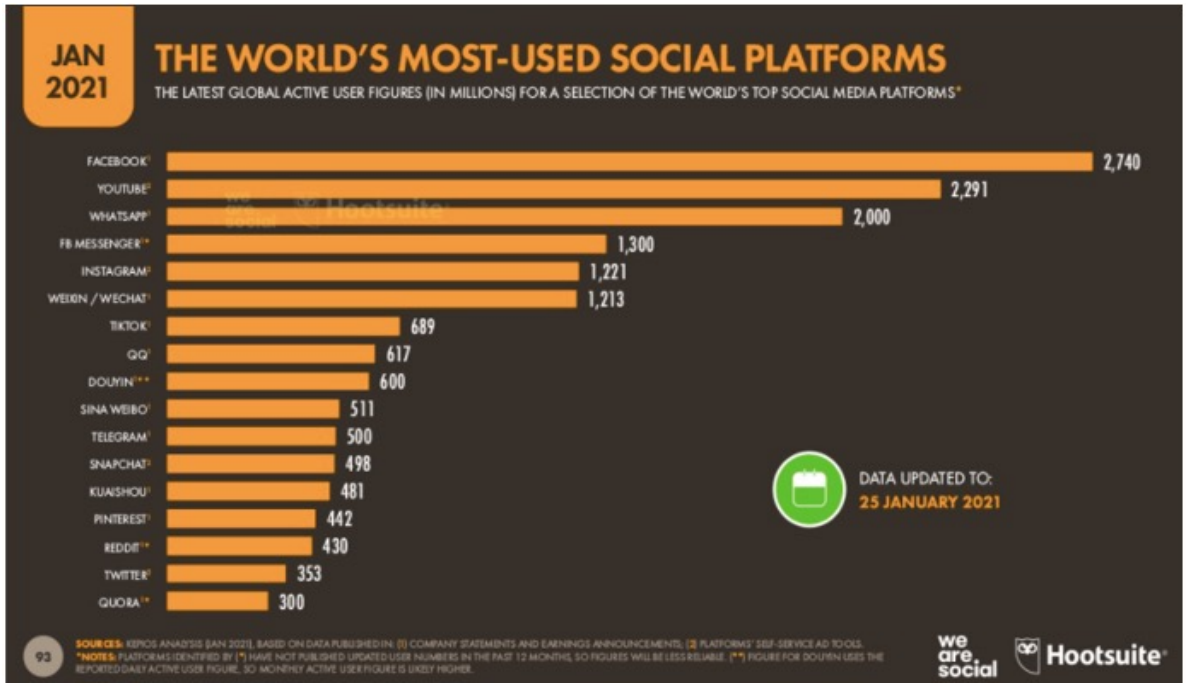
# Expansion of digital health technologies

Expansion of digital health technologies with global devices and smart phones availability.

| Use of Technology | 2010 | 2015 | 2020 |
|---|---|---|---|
| World population (in Billions) | 6.8 | 7.2 | 7.6 |
| Devices (in Billions) | 12.5 | 25 | 50 |
| Devices (per Head) | 1.8 | 3.5 | 6.5 |
| Total No of Smart Phones, Worldwide (in Billions) | 0.5 | 3 | 6 |

# Status of Social platforms

Most popular social networks worldwide as of January 2021, ranked by number of active users *(in millions)*

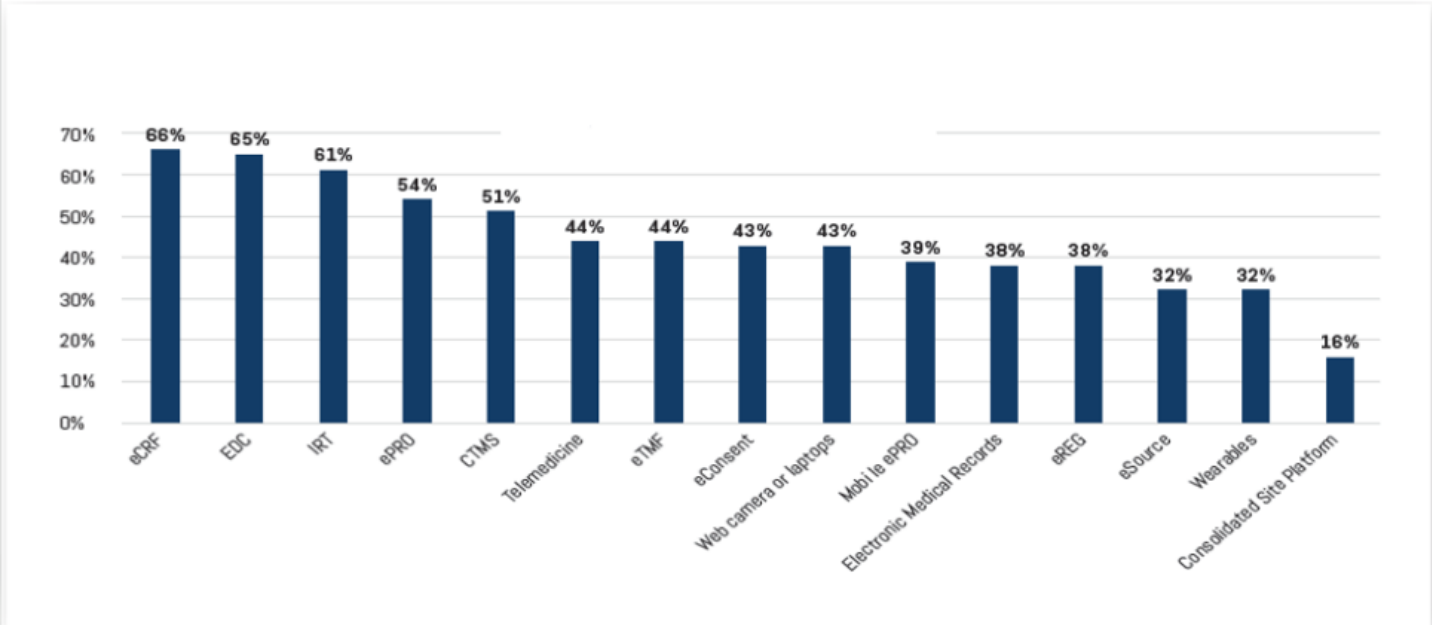


# Evolution of Data Driven Pharmaceutical Drug Development Process

Over the past forty years, the sources and usage of data supporting the drug development process have evolved substantially. Between 1980 and 2000, industry focused primarily on gathering scientific data which used retrospective, insular data sets that were small and had limited accessibility and utility. Since the turn of the millennium, industry has embraced gathering scientific and operating data to inform scientific questions and executional feasibility. This approach relies on more accessible and comparative data permitting interim review and adjustment. The enterprise continues to evolve toward patient centered data that requires open, flexible operating models supported by a high volume of structured and unstructured data, as well as powerful prospective and predictive analytics including those supported by machine learning and artificial intelligence. In the coming years, clinical development is expected to become increasingly decentralized, customized, and predictive.

| | 1980–2000 | 2000–2025? | Post-2025? |
|---|---|---|---|
| Primary mission | Great science | Feasible and great science | Patient-engaged science |
| Clinical trial orientation | Key Opinion Leadership (KOL) | Investigative site | Patients and patient data |
| Operating focus | Insular | Comparative and competitive | Open |
| Operating approach | Reactive | Responsive | Customized and predictive |
| Decision support | Basic and lagging | Risk-based, root cause and benchmarking oriented | Advanced analytics, leading |
| Data accessibility | Limited accessibility | Improving accessibility | High cross-platform accessibility |
| Data value | Retrospective, appraisal-based | Anticipatory, pre-approved, adaptive | Continuous, flexible learning |

# Current Processes and Technologies using in clinical trial operations



# New Digital trends in clinical trials

Some of the digital trends in clinical trials are described below:

1. eConsent
2. Digital Biomarkers
3. Patient selection and recruitment
4. Expansion of Telemedicine
5. eSource
6. Patient Centricity
7. Electronic Trial Master File (eTMF)
8. Wearables
9. Data Scrapping
10. Safety Monitoring
11. Drug Adherence
12. Digital Supply Chains
13. Recruitment of trial personnel through data analytics
14. Augmentation of brand value of organizations through social media

# Current trends in clinical data management

Now a days, sponsors are looking to modernize their clinical data management process on the following areas:

- **IT simplification:** Driving holistic programs focused on process reengineering and IT rationalization, and make the IT landscape leaner, smarter, scalable, well designed, incorporation of clinical standards and business optimization and future growth.
- **Data centricity:** Implementation of enterprise data lakes such as data repositories, investing in building capabilities in advanced analytics, and improving data quality and accuracy by adopting simplified and straight forward standard approaches and next-generation technologies.
- **Better collaboration:** Creating synergies between ecosystem partners such as technology partners, providers, preferred vendors, CROs, for better seamless trial data outcomes.
- **Change management:** Adopting forward-looking change and risk management solutions, and redefining and formalizing data management policies, procedures and SOPs etc.
- **People Empowerment and management**: Investing heavily in recruitment of skilled and experienced science/software personnel, onboarding, and training to incubate and inculcate new skillsets such as EDC, big data, artificial intelligence, machine learning, cloud infrastructure management, data standards etc.
- **Cybersecurity:** Building foolproof data governance structures to ensure privacy, security and ethical handling of clinical data including genomics data, HEOR data, and data collected through Bring Your Own Devices and other mobile devices.

# Additional famous digital trends in data management

The famous digital trends in data management are discussed below:

1. Artificial Intelligence and other smart and intelligent Automation
2. Data Analytics and Visualization
3. Data Strategies
4. Augmentation of Metadata Management
5. Blockchain in data and analytics
6. Interoperability

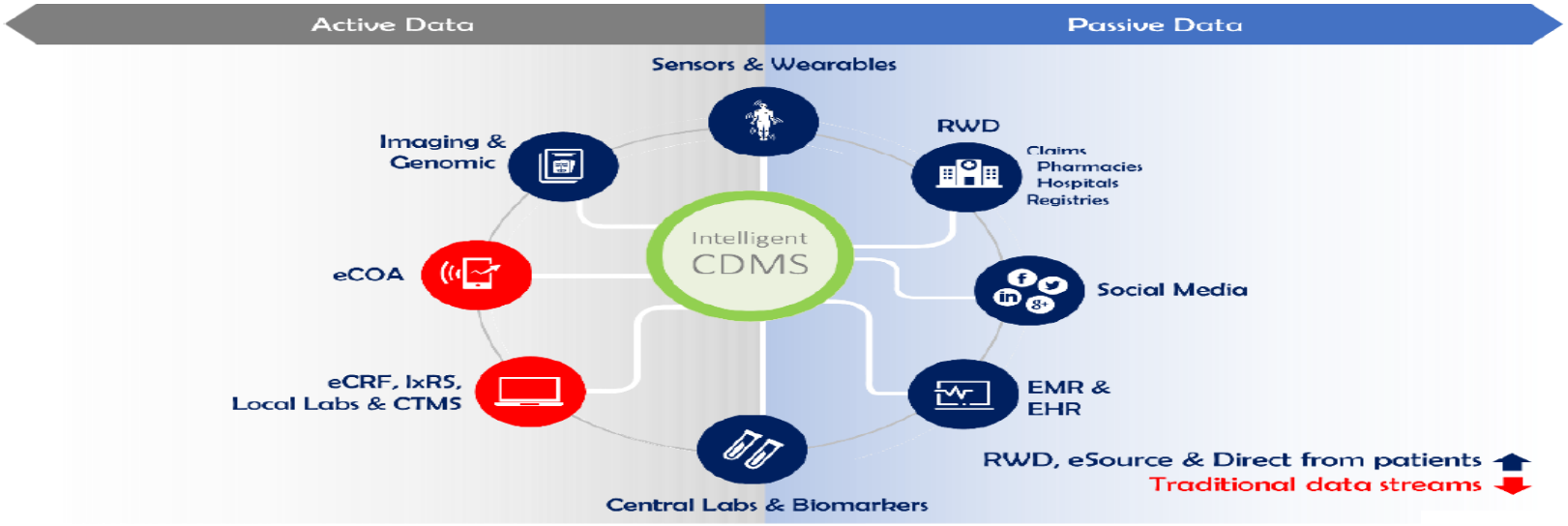
# Requirements of regulatory guidance

Some of the latest and future requirements of regulatory guidance on above issues are given below:

| Clinical trial issue | FDA 2020 guidance | Post-COVID-19 roadmap |
|---|---|---|
| Requirement of in-person consent. | Can obtain signed informed consent remotely. | Make electronic remote consenting permanent. |
| Requirement to use clinical trial–specified laboratories and imaging. | Allowed use of alternate laboratories and imaging centers. | Allow use of any laboratory and imaging center that meet specifications. |
| Recording of safety and clinical assessments based on in-person visits at investigator sites and investigator-based recording. | Allowed alternative methods for safety and clinical outcome assessments (e.g., virtual visits, phone contact). | Add Patient Reported Outcomes (PROs) and telehealth approaches to routine clinical trial methodologies. |
| Administration of investigational products exclusively at clinical trial sites. | Alternative delivery/administration methods of investigational products. | Increased use of community-based network sites as opposed to clinical trials sites only. |
| Requirement for in-person visits to receive investigational oral products. | Allowed home delivery of investigational oral products. | Direct-to-patient investigational product (oral drugs) and concomitant medication reporting via digital tools. |
| Requirement for in-person visits to receive investigational in-fusional products. | Allowed at-home or local health care provider infusion. | Aspire to 100% remote infusions and monitoring when feasible based on a risk assessment. |
| Limited clinical trial access for underserved populations. | Shipping of investigational product intended for infusion to a local health care provider for administration. | Decentralize clinical trial conduct and make it more accessible to rural areas and underserved populations:<br>• Increase funding mechanisms for trials conducted in underserved communities.<br>• Markedly broaden trials available for patients with wide range of comorbidities. |
| Requirement to administer "experimental clinical trial products" even if the same drug was approved and available commercially. Commercial procurement by patient of investigational product already. | Commercial procurement by patient of investigational product already approved for other indications. | Discuss mechanisms for use of clinical trial products obtained as commercially approved drugs. |

# Intelligent Clinical Data Management Systems

To support the 5Vs and be future proof, CDM needs a source and technology-agnostic data collection, consolidation and management strategy looking beyond the transfer of source data to EDC. This demands a new generation of CDMS (including data platforms, workbenches, reporting framework, etc.) which can interact with an end-to-end ecosystem of technologies supporting all emerging needs. CDMS must also manage ***active*** data from clinical research as well as ***passive*** data from medical care and personal health devices.



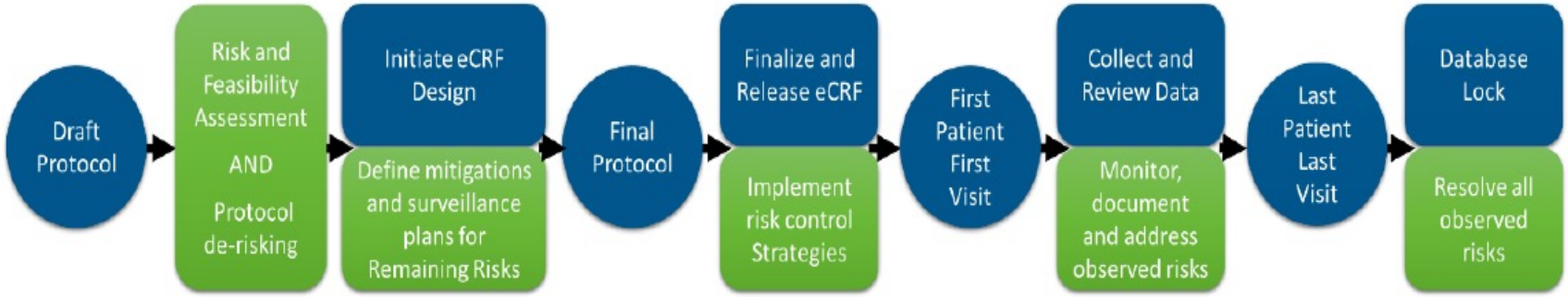
# Today's Global Data Management applications

## List of GCDMP Chapters

| GCDMP Chapters | |
|---|---|
| Data Privacy | External Data Transfers |
| Data Management Plan | Patient-Reported Outcomes |
| Project Management for the Clinical Data Manager | CDM Presentation at Investigator Meetings |
| Vendor Selection and Management | Training |
| Data Management Standards in Clinical Research | Metrics in Clinical Data Management |
| Design and Development of DCIs | Assuring Data Quality |
| Edit Check Design Principles | Measuring Data Quality |
| EDC - Concept and Study Start-up | Data Storage |
| EDC - Conduct | Data Entry Processes |
| EDC - Study Closeout | Coding Dictionary Management & Maintenance |
| CRF Completion Guidelines | Safety Data Management and Reporting |
| CRF Printing and Vendor Selection | Serious Adverse Event Data Reconciliation |
| Database Validation, Programming & Standards | Database Closure |
| Laboratory Data Handling | Clinical Data Archiving |

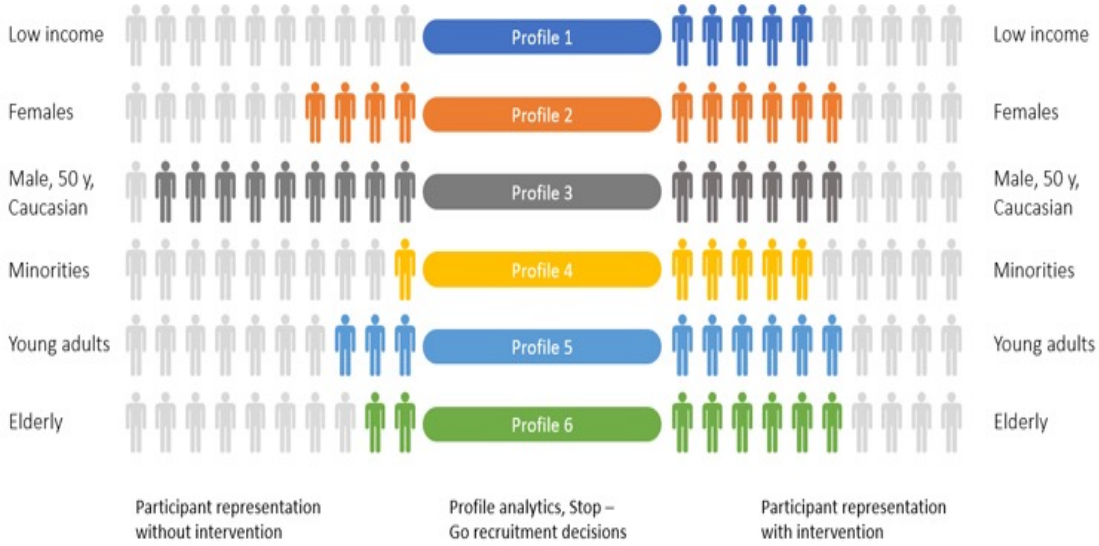
# Clinical Trial Management Platform applications

CDM must evolve substantially if it is to support QbD and risk-based study execution. This will have a dramatic impact on the CDS roles. Overall, the end-to-end management of the operational and scientific risks must be embedded throughout the entire process. Below is an example of a risk-based CDS process where new tasks depicted in green are added to the traditional CDM steps depicted in blue.

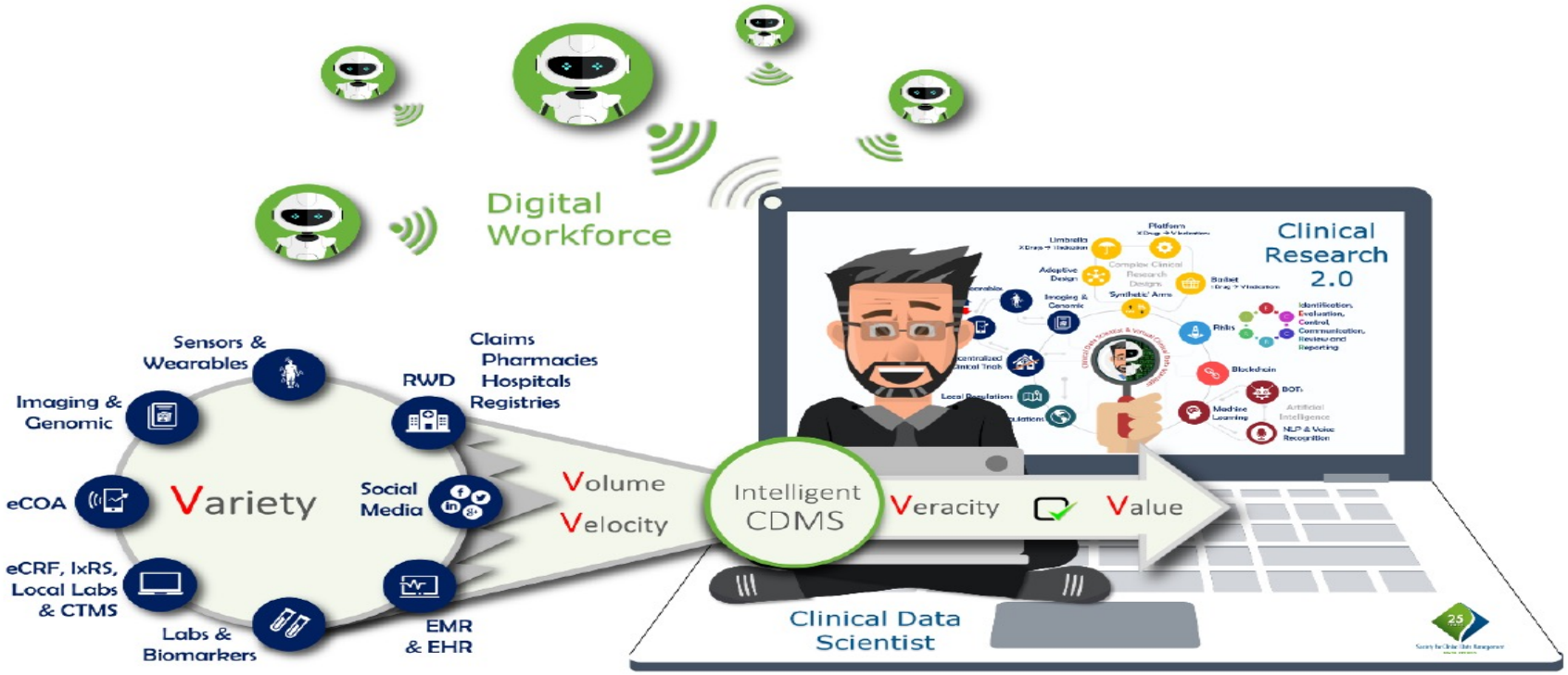


# Why is Data management turned into Data science?

Without data interoperability, we cannot get timely analyses that give us insights to make the right decision at the right time. Perhaps we aim to achieve a good diversity of recruited patients to resemble the target patient population that will use our drug once marketed. In real time, we need to know the profile of each patient being recruited in each participating study site and country and make the right Stop. Data management is turned into data science.

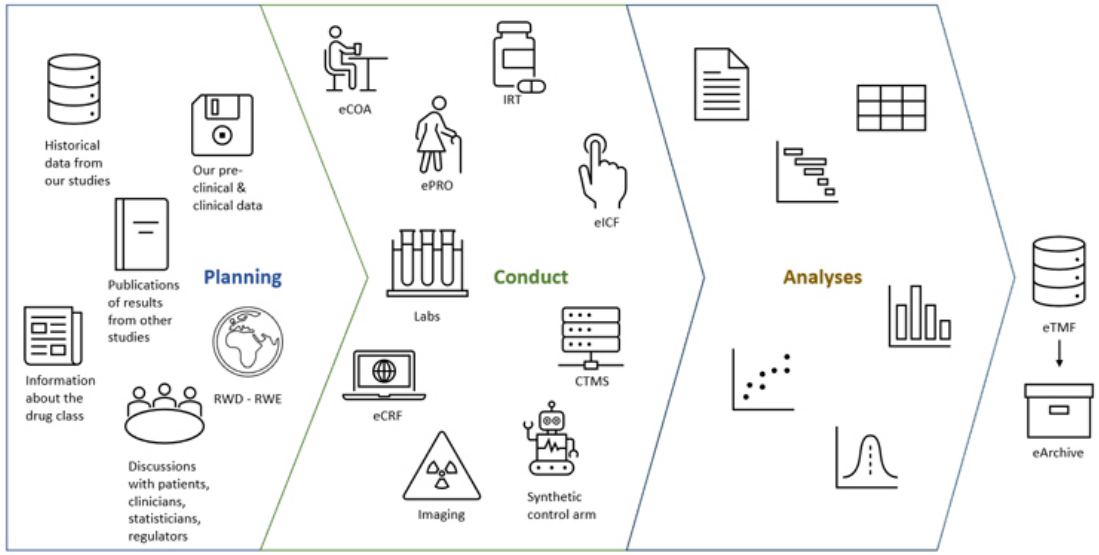


# Functions of Digital data scientist



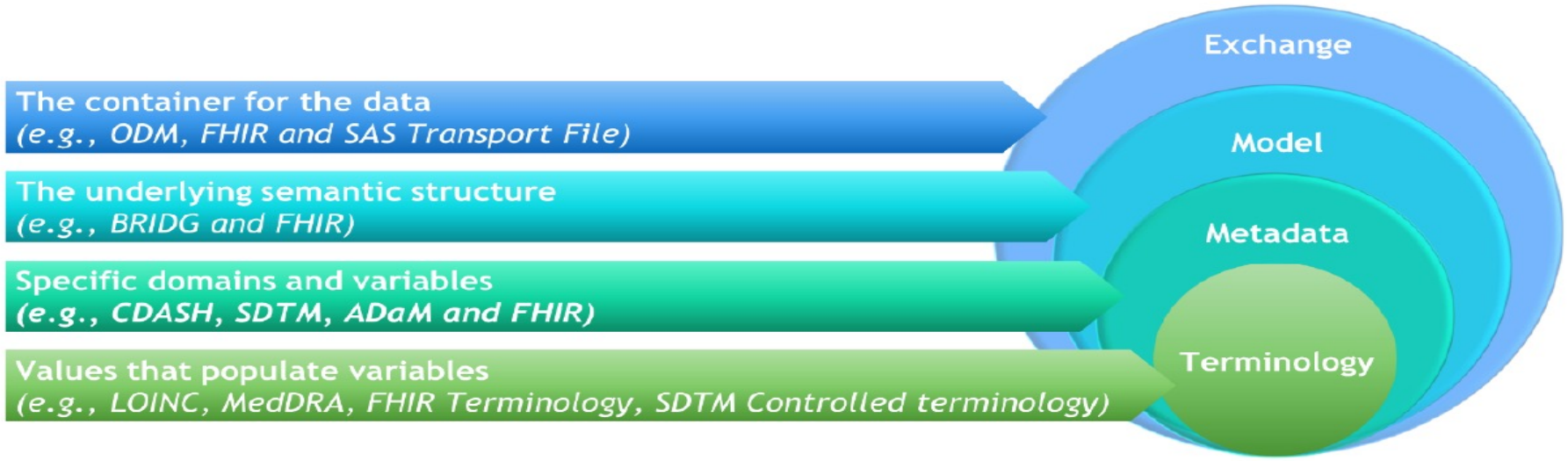
# Data Interoperability

The First Step To Leverage ML & AI In Clinical Trials is Data Interoperability. We must break data silos, find a way to make the data points communicate with one another within the drug development continuum, and analyze each data point in its full context. This is easier said than done. Data are coming from different sources, in different formats, including structured, semi-structured, and unstructured, with different levels of trust in their reliability depending on their provenance. We cannot forget appropriate governance, security, privacy protection, and ownership, which tends to be rather complex across multiple stakeholders.



# Layers of clinical data standards

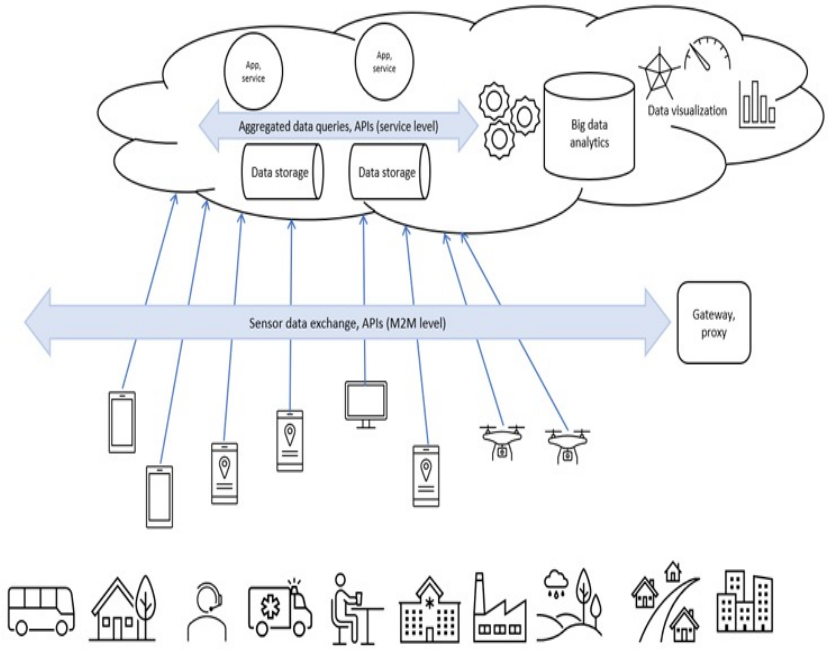
Standards can be classified in four layers providing synergetic values:
**Data models:** Conceptual, logical or physical semantic descriptions of objects and their relationships
**Metadata standards:** Representations of individual data concepts useful for organizing data in a database or data exchange file
**Terminology standards:** Representations of individual data values
**Exchange standards:** Schemas or file types for exchanging data between systems; the container for transporting data



# Ways to achieve Data Interoperability

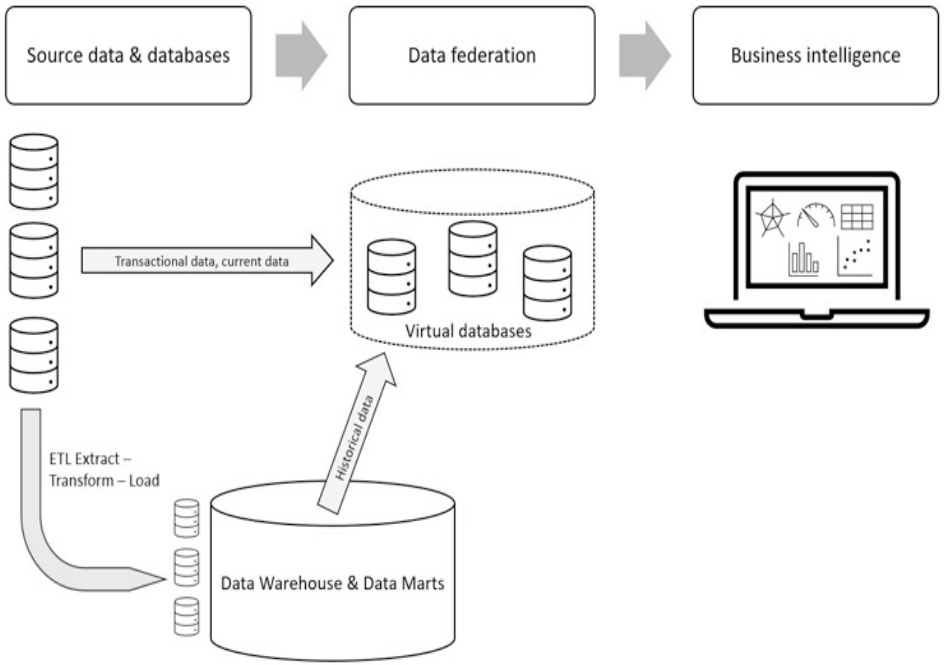
There are different ways to achieve data interoperability.

One approach advocates ***unified data formats***. If all data are in the same format, disparate data silos can easily merge into one large ***data lake or warehouse***.
Technically, it is feasible, at a limited scale.
There are many data formats; new ones are emerging and creating one unified format may result in losing important properties or attributes.
Instead of a unifying data format, we can use an ***application programming interface*** (API) to access the data. The API is placed as an overlay above all data silos or data-generating systems; it “talks” to each of them, works with metadata, uses all data without moving them out of their respective systems, and feeds analytical software and ML and AI applications.



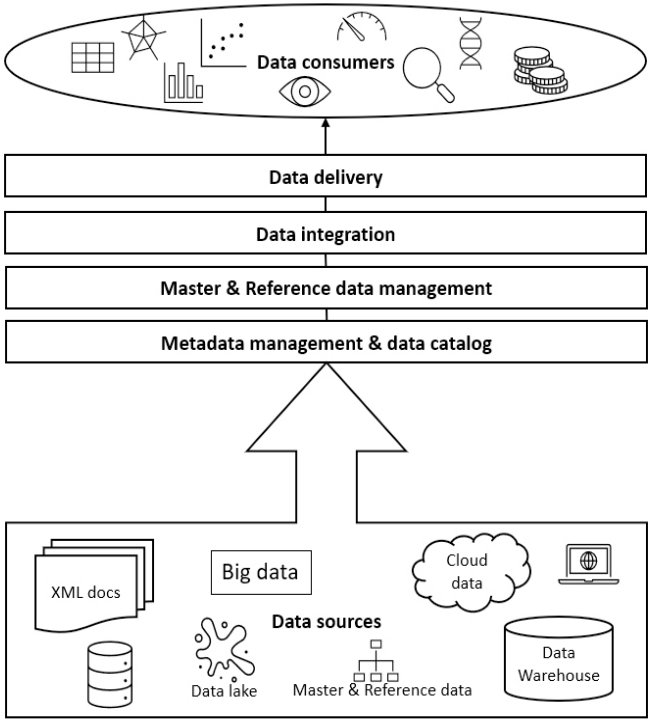
# Ways to achieve Data Interoperability (contd…)

The other possibility is to implement a ***federated database***. Very much like how independent states form a federation to become one country, we can combine autonomous data stores into one virtual federated database or data store. The advantage of data federation is that it enables us to bring together data from data stores that use different storage structures, different access languages, and different APIs. As a data consumer using data federation, we can access different types of database servers and files with various formats, integrate data from all those sources, transform the data, and access the data through various APIs and languages. Data federation is part of data virtualization, which includes metadata repositories, data abstraction, read and write access to source data systems, and advanced security.



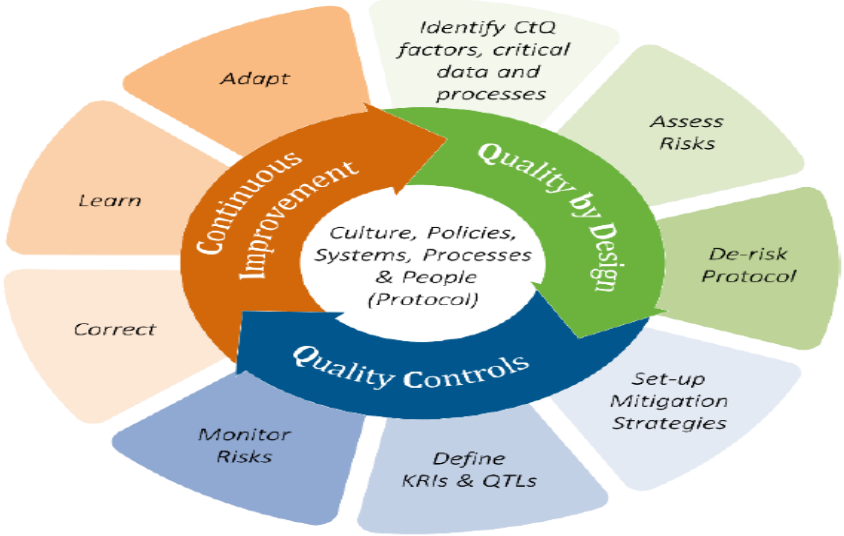
# The role of data integration in Data Management

If we work with very large data sets in a global company, we can consider an *end-to-end data integration and management solution* that will help us have all the data organized and accessible. This is what ***data fabric*** and/or ***data mesh*** do for us.
*Data fabric* consists of architecture, data management and integration software, and shared data, which provides a unified, consistent user experience and access to data for any company member worldwide in real time. Data fabrics creates relationships across various metadata points within disparate and even disconnected data sources allowing creation of and following specific relationship maps. In the healthcare data landscape, we can link patient care patterns in localized *electronic medical records* (EMR) with geographically specific *pharmacy claims data* and with overlapping *physician registry information* by zip code. It gives us the possibility to map specific physician-patient diagnosis and treatment with direct cost of care by treatment center and location. The specific connectivity between the disparate data sources does not have to be common data elements, or primary keys, such as in a data warehouse, but rather common metadata patterns that can be mapped or linked into a relational “fabric” across the differential data landscape.



# Risk based CDM approaches

Over the past decade, regulators have issued several guidance documents such as ICH E6 (R2)7 which define risk-based principles and advocate for the use of risk-based approaches. Embracing these methods, the industry has already successfully implemented risk-based approaches in the site monitoring and system validation spaces for several years. As a result, our traditionally risk-averse industry has become more comfortable with strategies that match efforts and focus commensurately to the risks.

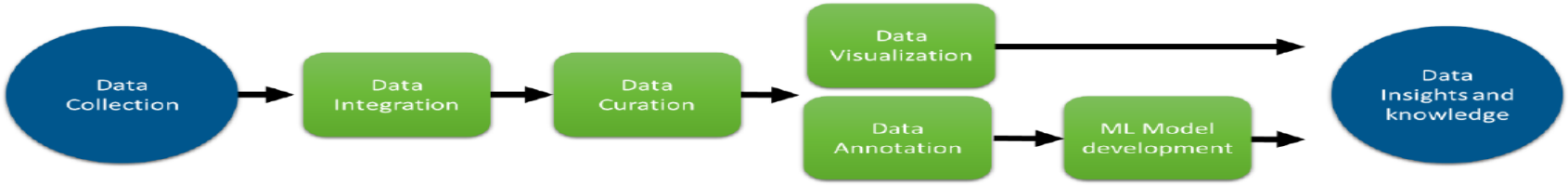


# Clinical data acquisition, standards and modeling

For Clinical Data Scientists, the most critical of the 5Vs is understanding the value of the data as not all data are created equal and will not bring the same value. Assessing how data sources will contribute to the primary objectives of the protocol is and will remain a core competency, however assessing the secondary value of each source and extracting the right evidence from it, whether it be for synthetic arm, translational research, and patient engagement will drive the focus of how that data is managed and the effort allocated to it. This is already being done for reimbursement by extracting real world evidence (RWE) from real world data (RDW).

# From data to knowledge data flow

**Data Integration Specialist:** The integration of data and knowledge from several sources is also known as data fusion. New data types are entering clinical studies regularly. CDS needs to evaluate new technologies including wearable devices using sensors. Further, they need to liaise with scientific and technology experts and be willing to explore new data types.
**Data Mining and Profiling Specialist:** Data mining and profiling are the initial steps in data analysis, where users explore a large dataset, structured or not, to uncover initial patterns, characteristics, and points of interest.
**Data Curator:** The curation of data includes its anonymization, integration, organization and exploration. The intent is to objectively confirm its integrity and quality to generate the appropriate secondary data assets such as RWE from RWD.
**Data Annotator:** The annotation of ideally curated data is the process of labeling the data available in various formats like text, video or images. For supervised ML labeled data sets are required, so that machine can easily and clearly understand the input patterns.
**Data Visualization Expert ("Storyteller"):** Data visualization is the graphical representation of information and data. Too often, visualizations have been limited to interactive but still basic descriptive statistics using simple graphs. Being able to tell a clear story from a large volume of data is crucial as insights are difficult to discover otherwise.
**ML Model Builder:** ML Models are developed and trained by leveraging statistical and programming methodologies. The developer must also lead the selection of the appropriate curated and if necessary annotated datasets for ML model training and testing.

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