# Innovation at the Intersection of Digital Health and Real-World Evidence

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# Understanding real-world data in healthcare and life sciences ecosystem

"Real-world data (RWD)" usually refers to patient-level observational data gathered when an approved medical product is on the market and used by patients in real life, as opposed to clinical trials. The U.S. Food and Drug Administration (FDA) cites several potential sources of RWD, including Electronic Health Records (EHRs), claims, disease and product registries, patient-generated data and data gathered from additional sources that can shed light on a patient's health status. These additional sources include the internet of things (IoT), social media forums and blogs.

# RWD evolving to digital health/big data

Advances in cloud technology, data science, and healthcare policies have resulted in tremendous growth in the volume, sources, and utilization of RWD with a collection of larger and more diverse data sets. The expansion in the use of Electronic Health Records (EHRs) and the proliferation of consumer digital technologies including mobile devices, wearables, sensors, adherence tools, social media platforms, and online patient communities have provided new data sources as well as improved means of capturing, storing and analyzing longitudinal RWD on patients.

The current RWD landscape is characterized by enormous variety and complexity. It extends beyond traditional sources such as chart reviews, prescription, or claims data to include both structured and unstructured data from a host of heterogeneous sources.

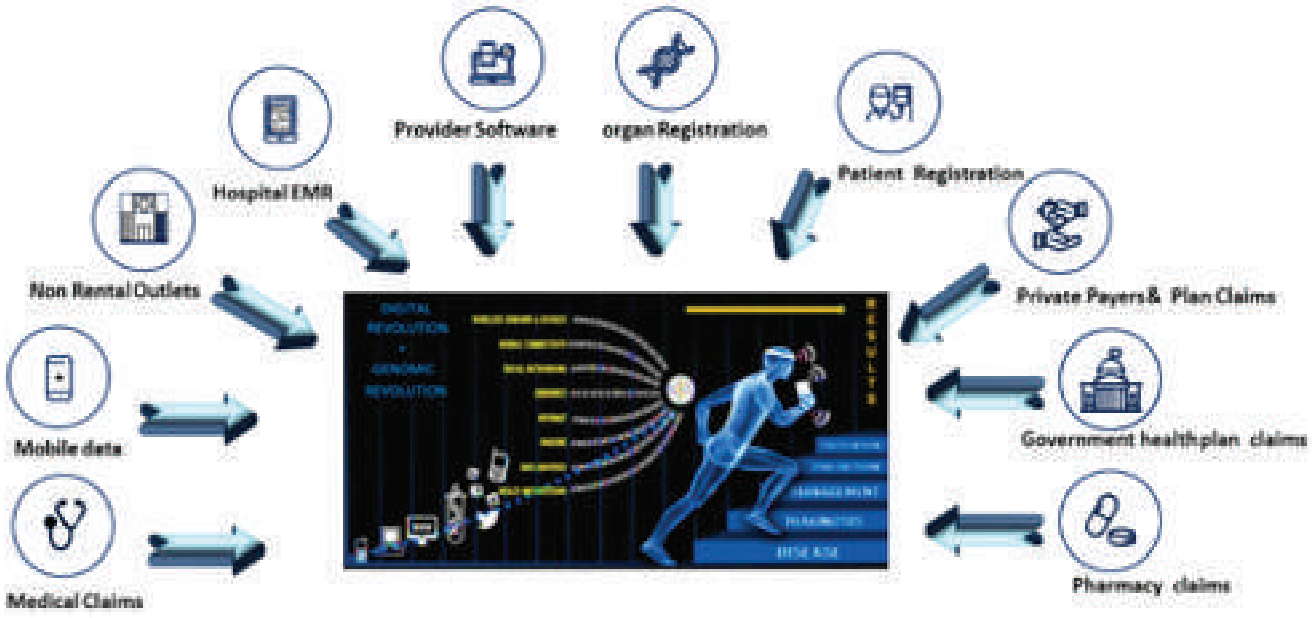


**Fig. 01:** Digital interactions between patients and health systems adds to complexity and rich data

# Major categories of real-world data

**Clinical data :** These are patient-level data pulled from electronic medical records (EMR) and patient registries that describe how patients are treated in the real world. They include lab values, diagnoses, notes, and other information from healthcare visits with physicians and other care providers. An upsurge in the amount of data from hospitals and entire health systems becoming digitized and more easily integrated across institutions, the power of these particularly rich datasets (for example, larger sample sizes, easier comparisons across systems) is increasing.

**Administrative/claims data :** Detailed patient-level data is also collected for non-clinical purposes, primarily for billing by providers to insurers and other payors, which can include diagnoses, services provided, costs, and other data required for the reimbursement of healthcare services. Other administrative sources of data are data collected for tracking purposes, such as patient or population surveys.

**Patient-generated/reported data :** This category covers individual data describing the patient's experience and is typically both collected and shared/reported by the patient. Today this source of data is less prevalent than others, but it might expand due to the increased use of wearable devices that automate data collection and sharing. Online communities such as PatientsLikeMe encourage and enable the sharing of patient-generated data with peers and investigators.

**Emerging data sources :** As digital becomes increasingly prevalent in our lives, new sources of patient-level health data are emerging.

Project Data Sphere is a pharmaceutical industry-sponsored platform to share, integrate, and analyse phase III comparator arm data from cancer trials to accelerate research. Also, online patient communities such as PatientsLikeMe and initiatives like PCORnet as well as consumer genetic services like 23andMe (Mountain View, CA) and uBiome (San Francisco, CA) have led to the rise of empowered patients who are more open and willing to share their health information for decision-making and research purposes.


**Fig. 02 :** The ever-expanding trove of real-world data sources

**"Real-world evidence" (RWE)** is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from the analysis of RWD. RWE can be generated by different study designs or scientific methods to inform decision making by healthcare stakeholders, including but not limited to, randomized clinical trials, including large simple trials, pragmatic trials, and observational studies (prospective and/or retrospective).

Generating evidence from RWD, therefore, depends not only on capturing "big data"- large volumes of these diverse data - but in effectively integrating these multiple and often disparate sources of data to obtain meaningful insights.

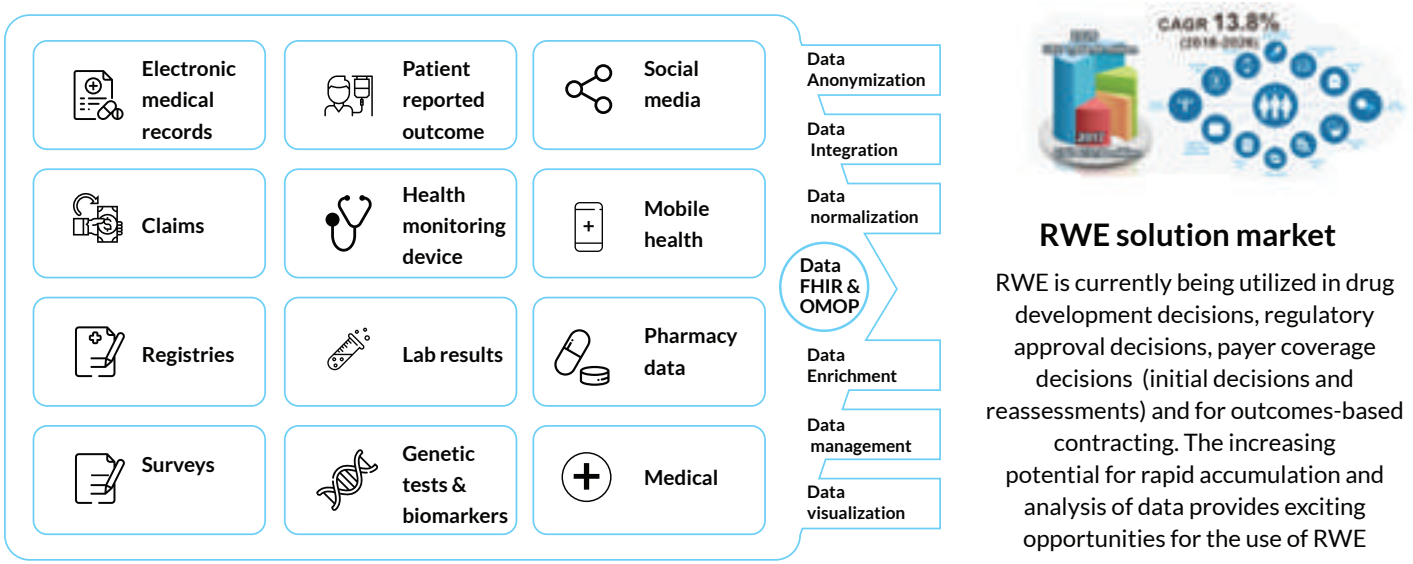


**Fig. 03 :** RWE Solutions market will see exponential growth healthcare value chain

## RWE beneficiaries and use cases

The importance of real-world data continues to touch all areas of our lives, with stakeholders across the entire healthcare value chain—physicians, providers, payors, regulatory bodies, patients and pharmaceutical, and medical device manufacturers—using real-world evidence to guide their decisions.

### Manufacturers

Tapping clinical trials optimization, Market access, Market assessment, the industry is a high consumer of RWE

**Some key notes**

- Evaluate effectiveness
- Secure reimbursement identify and understand unmet need
- Explore new indications
- Generate publication
- Add to safety profile

### Healthcare providers

Gain the ability to augment their intelligence on patient profiles, diagnosis, treatment pathway and potential adverse events

**Some key notes**

- How does the drug perform?
- Improve care
- Quality metrics
- Adherence
- Ensure reimbursement

### Regulatory agents

Traditionally FDA and EMA have used data for post – market safety and benefit/risk studies, FDA with 21st Care Act puts RWE as key enable for regulatory decisions and market approvals

**Some key notes**

- Safety
- Efficacy
- Long term effectiveness
- Does the drug do more harm than good in a defined population ?

### Patients

Being an integral participant of their own healthcare, patients will benefit from more data openness and availability, enabling as personalized medicine

**Some key notes**

- Willingness to pay out of pocket
- Quality of life
- Safety
- Convenience
- Affordability

### Payor

Manage cost of care and coverage, RWE also enables insights and decisions for personalized reimburse-ment models based on usage, value and outcome

**Some key notes**

- Health cost and consequence relative to other interventions
- Determine value and coverage
- Monitor usage within criteria
- Risk-sharing
- Quality metrics

**Fig. 04 :** RWE Solutions market key beneficiaries

# Payers

RWE is of immense relevance to the payers, who by definition have this data through the claims they receive. but there is growing pressure from payers to gather more outcomes-based RWE to help them determine what they should continue to pay for.

Budget pressures are driving HTA bodies and payers to use RWE in conjunction with evidence from clinical research to inform reimbursement decisions. The need to price drug products based on the value offered to patients is reflected in value-based contracts between pharmaceutical companies and payers to link the price of a prescription drug to its clinical and economic performance. Payers are positively disposed to use RWE, but knowledge gaps around the validity and value of RWE must be closed to improve access for rare disease patients.

### Existing and emerging use cases for using real-world evidence by payers

• RWE currently used by payers is outcomes-based contracting
• RWE insights enable effective coverage decisions and price negotiations for payers
• HTA assessments & payer coverage decisions
• RWD can facilitate the creation of larger cohorts of patients with rare diseases where patients are extremely difficult to identify
• By integrating claims with EMR data to generate insights into the value and effectiveness of providers or protocols
• Payers need to use these RWD-enabled analyses to drive conversations with pharmaceutical companies regarding prices for therapies and appropriate payment models

Ex: undertake analyses of the relationships between the surrogate endpoints reported from randomized clinical trials, and the true clinical endpoints available in larger RWD repositories, the use of these data sets can overcome the limitations of clinical trials.

Payors are using outcomes-based contracts with providers and patients pay for good outcomes.

# Provider

Value-based payment reforms contain direct provider incentives that rely on the collection, reporting, and analysis of RWD to assess and improve provider performance based on approved quality metrics. Physicians and providers rely on electronic medical records (EMR) data for physician-led clinical research while health system administrators use the same data to monitor the quality of care delivered across the system, including monitoring adherence to care pathways. With the growth of EMR, physicians can now quickly access the same data across a larger number of patients and institutions.

### Existing and emerging use cases for using real-world evidence by providers

• Influence on evidence-based medicine, personalized and effective healthcare
• Applying "big data" to improve patient care guidelines and manage formularies
• Managed care applications seamlessly integrate the cost of therapy with patient-generated records creating immense potential for enriching RWE study
• Clinical decision support that gathers RWE on treatment outcomes along with genomics data to allow clinicians to assess outcomes by patient cluster

# Manufacturer

Pharmaceutical companies have rapidly progressed in their use of real-world evidence. Initial years limited the use of RWE and was heavily focused on safety and post-market. Nextgen efforts saw more integrated use of RWE across the end-to-end product lifecycle during which it was deployed to support regulatory decisions, advance disease understanding and clinical guidelines, and outcome-based reimbursement decisions.

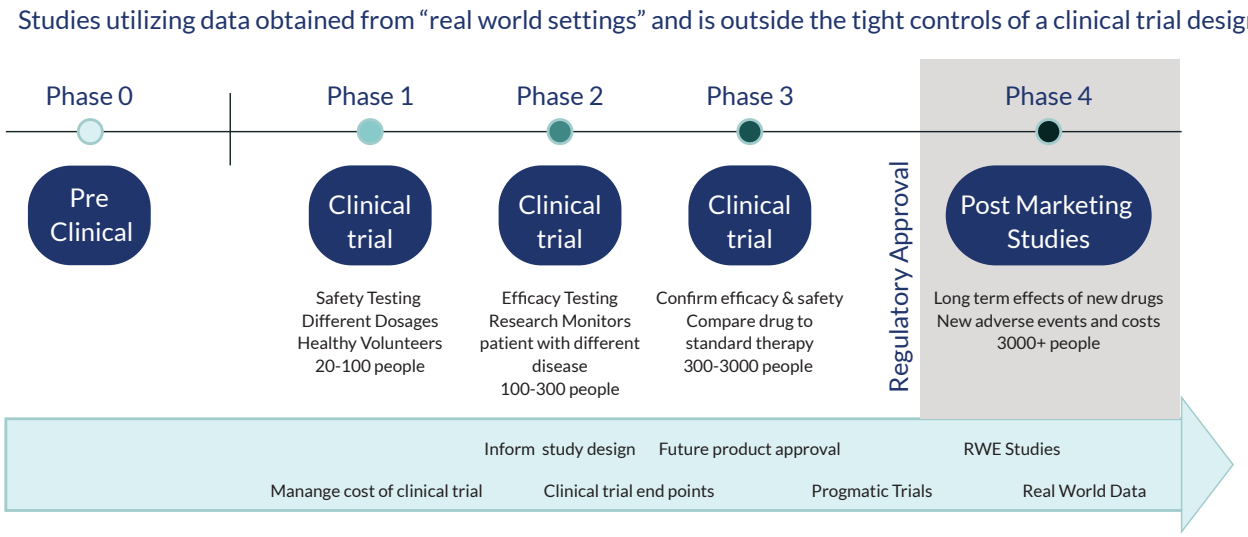


**Fig. 05**: Evidences based on data from real world settings falls outside the tight control of clinical trial design

**Impact on drug development:** RWE has immense potential for drug developers and scientific community allowing personalized medicine and providing info on resource utilization and financial cost of implementing a therapy or treatment which is also very important for providers, patients, and payers.

Pharmaceutical companies take several years to introduce a new drug molecule to market, and they invest billions in research and development with a low probability of success. To shorten the drug development cycles, pharma research centres need a clear insight on treatment options that work in a wide population compared to few patient pools in clinical trials. The use of RWE insights is thus found increasing as pharma and biotech companies realize that RWE can be important in drug development and life-cycle management and increase efficiency in innovation and cost of clinical trials.
The use of electronic monitoring devices coupled with the provision of feedback to patients of their recent dosing histories is an evidence-based approach to enhance patient adherence to medications.

## Existing and emerging use cases for using real-world evidence by manufacturers

- Addressing the limitation of the randomized controlled trial (RCT) with Pragmatic clinical trials (PCTs) offers the advantages of randomization combined with the added relevance of results obtained in more real-world clinical settings. PCT adds the richness and complexity of drug efficiency for a larger population complementing clinical trials which has inclusion/exclusion criteria very suitable for benefit-risk evaluations of drug development

Ex: Hyperglycemia study – Uses Predictive modelling and AI methodologies identify the efficiency of insulin and compare Nextgen insulin

- Using RWE analysis reduces the cost of drug development by favourably impacting the efficiency of planning and operations
- Enables real-time decision making to protect public safety, such as taking swift action when RWE shows adverse events that weren't detected in clinical trials

- RWE can also be leveraged for real-time strategic decision making to support a brand, Using the "real-time" intelligence, companies can act quickly
- Epidemiological data helps to identify targets for the development of new therapies and can help to make inform decisions around the most appropriate drug development pathway
- Modelling and extrapolation approach for dose-finding (e.g., from pharmacology and toxicology data)
- Use of simulation/modelling approaches to eliminate the need for additional clinical studies (e.g., in assessing drug-drug interactions)
- Novel design and statistical considerations in rare disease drug development
- Trials incorporating real-world evidence controls
- Modelling disease progression from natural history data
- Many-to-one matching methodologies, allowing comparison of one study subject with several historical controls

# Regulators

The passage of the 21st Century Cures Act ("The Act") by the US Congress in December 2016 opened up a new pathway for pharmaceutical companies to leverage RWD in the development and expansion of indications for their products in the United States, which was reinforced in the Prescription Drug User Fee Act (PDUFA) VI authorization. The Act clearly defines a role for RWE in the regulatory process by mandating that the US FDA must issue guidance describing how pharmaceutical companies may use RWE:

1. To help/support the approval of a new indication for a drug approved under section 505(c)
2. To support or satisfy post-approval study requirements

This has significant implications for both the cost and speed of drug development. Pharmaceutical companies have sought to utilize combinations of multiple existing registries to satisfy post-approval safety study (PASS) requirements in both US and EU contexts.

The use of RWE and  RWD is also an increasing priority for other regulatory authorities other than the FDA.

**Existing and emerging use cases for using real-world evidence by regulators**

- Post-approval monitoring of safety signals and take regulatory action if necessary
- The role of data extrapolation from varying age cohorts: Regulatory requirements for pediatric/rare disease drug development
- RWE can be leveraged for regulatory decision-making related to label extension or to support a new indication for an approved drug, as well as to substantiate confirmatory evidence for drugs approved under the expedited regulatory programs (ex: epidemic like covid19)
- Opportunities for single-arm trials to be implemented and evaluated through the concept of "threshold-crossing. In this model, an efficacy or safety threshold is established as a benchmark for a new drug via the use of RWD, and if this threshold is achieved the new drug can be considered successful and can forgo RCT evaluation. If unsuccessful, a traditional RCT is established
- **RWE to establish historical controls :** When patients cannot be randomized to placebo such as in life-threatening orphan diseases with no adequate therapeutic options, historical controls are needed. Before the advent of EMR, physicians would physically scour old patient charts to build historical controls for regulatory submissions. Now with the advent of electronic medical records, this patient-level data can be assessed on a larger number of patients more easily and effectively.

# Barriers and solutions to enable use of real-world data

RWD offers significant opportunities for improving healthcare landscape, innovation, and decision-making, as with any rapidly evolving field there are challenges to leveraging its full potential. These challenges range from technical (e.g., claims data are collected for administrative billing purposes are now envisioned to support drug development decisions), to ethical (a risk to privacy as health information and patient data sets are aggregated), to analytical (selecting which RWD are appropriate to informing a particular decision, and reducing the risk of bias). The most significant barrier to expanding the use of real-world data is the consensus that randomized controlled trials (RCT) remain the gold standard for demonstrating the efficacy and safety of medical products and treatments. This consensus, shared by physicians, patients, payors, and regulators alike, creates significant hurdles to using RWE, In addition to the preference for RCT, other barriers to developing and using RWE exist and need to be addressed to realize the potential of this data source.

# Data quality

The data collection is episodic, reactive, and at best offers a partial picture. As a result, RWD is in general messy and sparse and requires statistically rigorous and valid methods to clean the data and correct inconsistencies. Data curation, using both structured and unstructured data, is especially important for precision therapeutics in oncology, where often crucial information related to molecular biomarkers or end-points data can be missing.

Missing data may also need to be filled by linking to alternative data sources. Analysts must also identify and adjust confounding factors such as demographics, socioeconomic and insurance status, disease severity, comorbidities, concomitant medications, and genetic predispositions to certain conditions before conducting in-depth analyses. RWD is also subject to selection bias, as cohort selection and treatment decisions in clinical practice are not random. Therefore, following appropriate guidelines on the design and validation of RWE studies can help in minimizing some of the sources of bias and inconsistencies.

# Interoperability

Industry standards for the development and maintenance of data assets have not yet caught up with the rapid evolution of RWD, even within individual organizations, there is often a lack of consolidated or centralized data storage, leading to difficulties in analysing data across different data sets.

The answer lies in leveraging common data models, integrated delivery networks are looking at how they might adopt the research-centric Observational Medical Outcomes Partnership (OMOP) common data model, as well as the Clinical Data Interchange Standards Consortium's (CDISC) Study Data Tabulation Model (STDM) standard for regulatory submission. And across all of healthcare, the Fast Healthcare Interoperability Resources (FHIR) specification is gaining greater traction to enable the exchange of EHRs. Linking these standards efficiently to enable better data access, improved data quality and greater insights at speed will be a game-changer in the RWE world.

Health Level 7(HL7) and IMEDS are creating standards for electronic health data and promoting interoperability among systems. Advances in data standardization, interoperability, and linkage techniques are anticipated to further enable disparate data sources to converge into a single platform for more seamless and efficient analytics.

# Analytical platforms

Even though the adoption and use of EHRs have grown significantly, extracting meaningful data from EHRs accurately and efficiently remains challenging. This is since a significant portion of high-value clinical information in EHRs is often stored in unstructured, free-text clinical documents that are inaccessible to algorithms and require layers of pre-processing. For example, even a frequently used metric such as the ankle-brachial index (ABI)—a "quantitative" data point for defining peripheral arterial disease (PAD), is typically embedded in the text of radiology reports, hidden from structured data analytics tools.

Natural Language Processing (NLP) methods provide one approach for the extraction and conversion of unstructured information from clinical text data to structured observations. Further, predefined fields in EHR (e.g., problem lists, history, or test result fields) capture only certain disease information and may miss the trends of other prevalent, but unlisted, health conditions. NLP can be a powerful tool to extract symptoms from physician notes or textual data from lab reports to enable identification of those trends/conditions, thus complementing the assessments using structured data.

# Conclusion

In conclusion, RWD and RWE have the promise to strengthen the current ecosystem of data supporting healthcare decisions, and support transition into a new era of personalized, more effective, and more efficient health care. Collaboration among providers, patients, payers, drug companies, and other players in the healthcare system, aided by technology, would be necessary to unleash a new age of medicine.

Within the broader healthcare ecosystem, the emphasis is increasingly on breaking down the inefficiencies and information silos between the different players. The goal is to streamline processes to support value-based care and develop new pharmaceutical and medical devices to improve outcomes and reduce costs. But for this to happen, healthcare organizations must achieve more efficient data integration to realize a true and complete view of patients and their data. A significant elevation of frontline capabilities across medical affairs, commercial, development, and health economics and outcomes (HEOR) will be required to share these analytics in a compliant and impactful way.

Understanding the key drivers for RWD and RWE solution outcomes will lay the foundation for analytical consumption and Companies that can quickly and easily utilize data-driven RWE solutions will win in the marketplace.

**Big data :** Increasing availability of multiple disparate data sets from both traditional databases, primary RWD, such as registers and novel data sources (i.e. EMR free text, social media, biosensor, mobile apps etc.) requiring innovative technology to aggregate, curate and analyse.

**Advances in Health technology :** cutting edge technology platforms evolving at a rapid pace. Platforms that are designed for electronic data capture, storage and management of EHR data with the ability to accommodate structured, semi-structured and unstructured data, accommodate structured, semi-structured and unstructured data, NLP capabilities and ability for data streaming from a variety of devices.

**Technology Companies Disrupting Healthcare Space :** willingness and ability of new players to collect, aggregate and access healthcare data. Proliferation of start-ups with new technologies. Third party data aggregators. Large technology players data aggregators. Large technology players co-developing data with health care data providers.

**Companies harnessing technology to maximize RWE value :** Increased effort by large pharma companies to build their own technology infrastructure and bring together both technology and the expertise of RWE specialists to optimize a fully integrated and holistic approach.

**Uptake in Cross Functional Evidence Based Decision Making :** need for platforms to accelerate the adoption of RWE across the full spectrum of users in making sales, HEOR and R&D functions and enable on-demand RWE insights. Companies looking at how they can leverage RWE across the enterprise for maximum value.

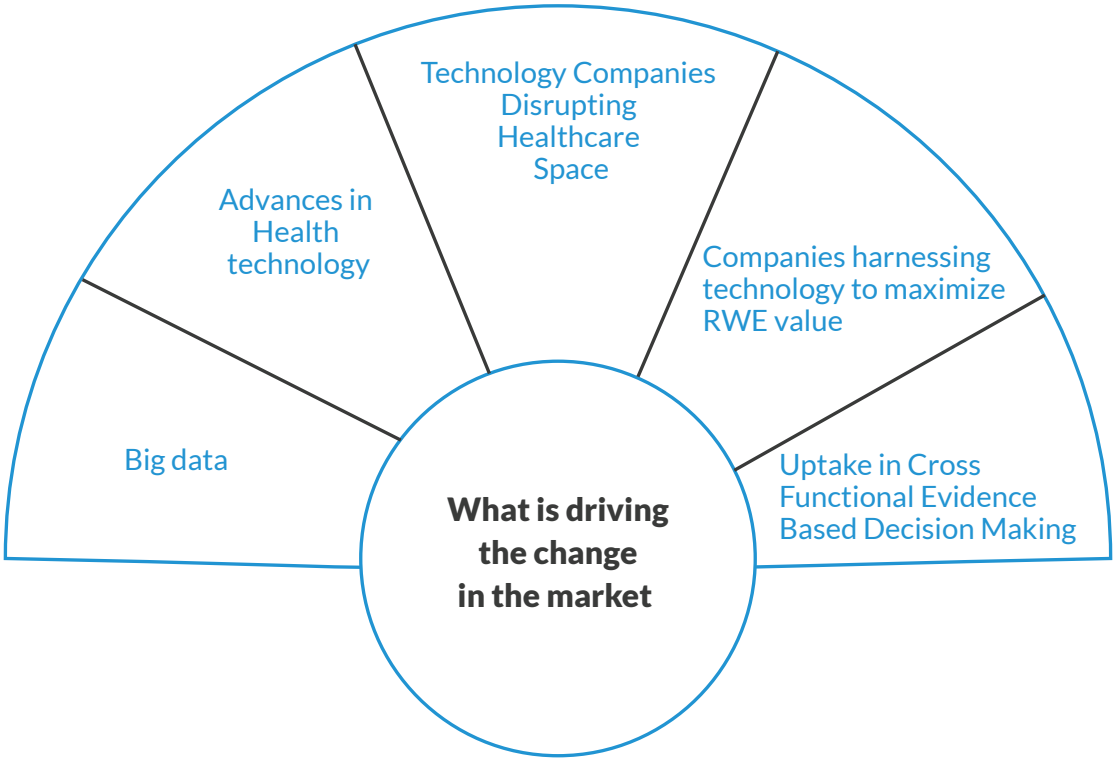


**Fig. 06 :** Key technology drivers influencing RWD and RWE solutions

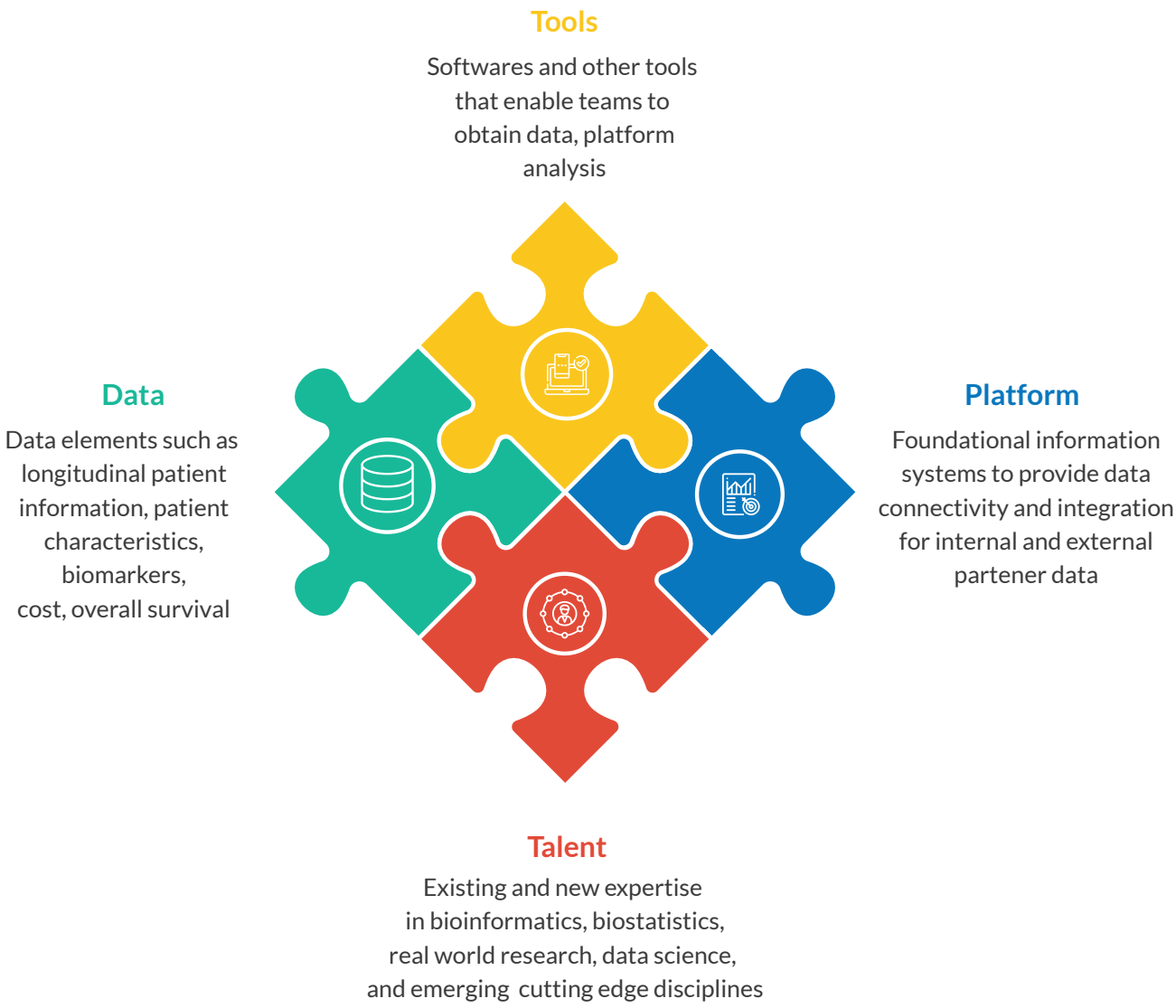


**Fig. 07 :** Achieving digital health will require new capabilities

**Shaping an integrated, adaptive partner ecosystem** : Companies will need to identify expert collaborations to ensure credibility and trust in analyses, as well as gain access to novel data sources. Unbiased experts are needed to address short-term concerns around the credibility and trust of these analytics. Companies may also need to consider partnerships with subject matter experts that have defined roles, such as in analytics and building platforms at scale to manage and analyse data in a rapid, low-cost fashion.

**Write to us at analytics@ameexusa.com to know more about our expertise in the pharma and health-care industry.**