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WHITE PAPER

BRINGING IN VITRO DIAGNOSTICS TO MARKET WITH REAL-WORLD EVIDENCE

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Summary

In vitro diagnostic (IVD) devices are a unique type of medical device. Although they meet the definition of a medical device, they are not intended to treat a disease or condition. Rather, they are the instruments or reagents that analyze samples taken from patients. IVDs are less invasive than traditional medical devices, but still present a risk to a patient.

This white paper examines some of the unique aspects of IVDs in an ever-changing regulatory landscape, presenting the concept that real world evidence (RWE) shows promise in optimizing the regulatory decision-making process to bring IVDs to market.

Recent, Sharp Rise in In Vitro Diagnostics

During the COVID-19 global pandemic, there was a sharp rise in IVDs for rapid testing using polymerase chain reaction (PCR), next-generation sequencing (NGS), and serology. The pandemic saw a rise in molecular assays, particularly real-time polymerase chain reaction (RT-PCR) testing, to meet the demand for faster, higher volume testing. In 2019, it was estimated the molecular diagnostics market in the U.S. would grow an average of more than six percent every year for the next five years.[1]

The response to this challenge of meeting such high demand led to accelerated development of even more diagnostic technologies, such as NGS and CRISPR, under emergency authorization. NGS has been used prevalently in precision medicine, but the pandemic allowed NGS to be used in large-scale, high-volume diagnostics.

By 2027

The IVD market will top $140 billion.[2] Cancer diagnostic testing is among one of the fastest growing tracks, with cancer biomarkers, immunohistochemistry, and molecular testing among the fastest growing.

Other areas of growth include substance abuse, immunoassays, cardiac markers, and point of care tests for inherited diseases.

Unique Nature of In Vitro Diagnostics

IVDs have some unique aspects compared with traditional medical devices. Here are the main differences:

- The safety profile of IVDs is tied closely with their effectiveness, presenting challenges to regulators who make decisions on how accurately an IVD will detect a disease or condition
- The U.S. Food and Drug Administration (FDA) has been revisiting the level of regulatory oversight, adding another layer of complexity to regulatory decisions. As a result, there is a need to revisit the way patient safety of IVDs is evaluated
- IVD technology is quickly evolving
- The current state of RWE for regulatory assessment holds the promise of optimizing regulatory decision making and potentially reducing costs of bringing products to market

Laboratory Developed Tests (LDTs) are a special subset of IVDs intended for clinical use within a single specified clinical laboratory that meets requirements under the Clinical Laboratory Improvement Amendments (CLIA) regulations.

LDTs fall under the definition of medical device and are subject to regulatory oversight by the FDA. However, historically, FDA has exercised enforcement discretion over LDTs.

A laboratory is required to establish certain performance characteristics relating to the analytical validity of the test they are proposing. These performance characteristics, however, have been limited to the controlled conditions of the single laboratory, designated staff, and equipment.

Analytical risk is evaluated based on the risk to the patient of a false positive or false negative result. If the patient's risk is high, then clinical performance is often required with a premarket submission.

Performance in the clinic is critical as it provides insight into the clinical relevance of the diagnostic device needed for making patient-focused decisions.

Designing In Vitro Diagnostic Studies: Advantages and Disadvantages

Designs of IVD medical device clinical performance studies are either observational or interventional.

- An observational study refers to a study in which test results obtained during the study are not used for patient management and do not impact treatment decisions
- An interventional study refers to a study in which test results obtained during the study may influence patient management decisions and may be used to guide treatments

The majority, though, follow an observational design meaning they are not used to determine patient management decisions as they are done in parallel to routine diagnostic testing. This type of clinical validation study, referred to as a clinical performance study, evaluates whether the IVD medical device is suitable for the purpose(s) and the population(s) for which it is intended.

Observational studies can be cross-sectional, longitudinal, retrospective, prospective, or prospective-retrospective. Choosing the right study design depends on factors such as the study objectives, the intended use of the IVD device (test purpose, target population, etc.), and the statistical design.

While the randomized controlled trial (RCT) has been the gold standard with trial design, there are advantages and disadvantages to this option. The difference between randomized and nonrandomized studies is that in the former, the investigator allocates the interventions to participants randomly. Randomization prevents the skewing or deliberate manipulation of results. Both participants and research scientists can influence results unless the researchers assign participants to groups at random.

RCTs are investigations like cohort studies in which the researcher randomly assigns exposure or intervention to the study participants. The aim of clinical trials is to investigate the effectiveness and safety of an intervention. RCTs are widely regarded as the optimal approach in assessing a new treatment.

All RCTs, like device trials, share common core design features such as explicit inclusion and exclusion criteria, use of controls, randomization, masking where feasible, and the intention-to-treat principle.

Heterogeneous populations captured in data sources can provide additional insight into diverse and underrepresented groups to support the generation of evidence that can help address disparities in healthcare access, treatment, and outcomes.

Advantages

The main purpose of random assignment is to prevent selection bias by distributing the characteristics of patients that may influence the outcome randomly between the groups, so that any difference in outcome can be explained only by the treatment. RCT gets rid of selection bias by removing the element of choice. Thus, random allocation makes it more likely that there will be balancing of baseline systematic differences between intervention groups regarding known and unknown factors such as age, sex, disease activity, and duration of disease that may affect the outcome.

For clinical trials, real-world data (RWD) can improve recruitment and representativeness through precision recruitment, streamlining screening criteria, and identifying barriers to trial participation. Pragmatic or decentralized trials can also leverage RWD to improve sampling frame size and diversity.

Disadvantages

A control group in RCT helps reduce the likelihood of any benefits or risks the researchers identify during the trial that may occur due to factors outside the experimental treatment.

Furthermore, not all scientific questions can be answered by RCTs given cost limitations, ethical concerns, or pragmatic limitations. In these instances, RWD can be leveraged to conduct trial emulations, or other forms of secondary data analyses of effectiveness and long-term analyses of risk factors.

Real-World Data Approaches for Real-World Evidence

Traditional clinical trials can have strict inclusion criteria, posing challenges for providers to accurately extrapolate the results of a clinical trial to a broader population. Because clinical trial participation is often limited by who the study administrators can recruit, and various demographics are often not able to participate, this approach again challenges the generalizability of clinical trial results across patient populations.

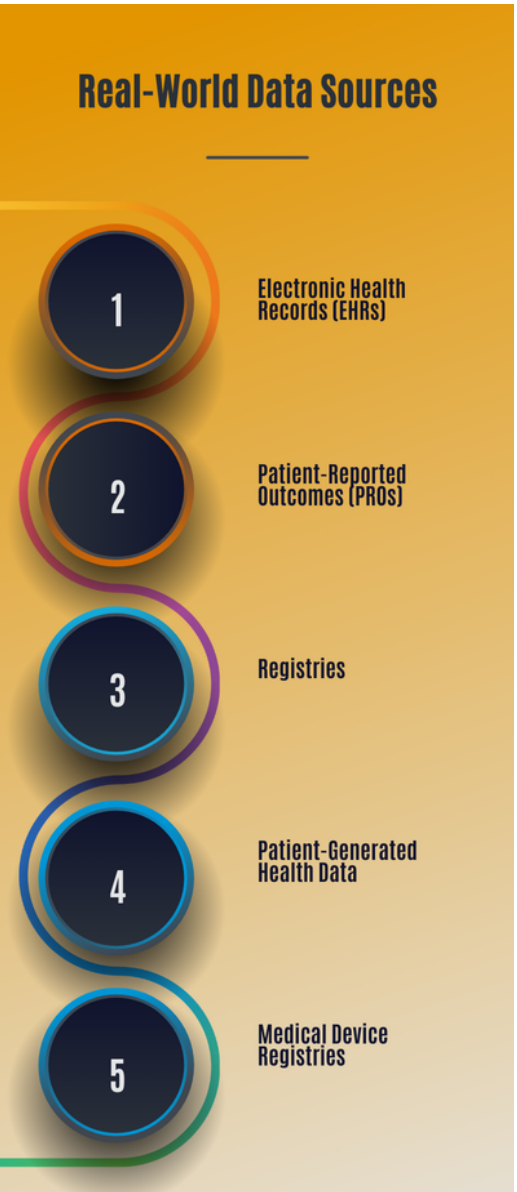
But in recent years, regulators have placed a growing emphasis on patient centricity in clinical trials and IVD trials are no exception. In fact, the FDA issued a series of guidances on using RWD from patient-reported outcomes (PROs) to ensure a more patient-centric approach to IVD studies. Guidances include:

- Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices[3]
- Patient-Reported Outcome Measures: Use in Medical Product Development to support Labeling Claims[4]
- Principles for Selecting, Developing, Modifying, and Adapting Patient-Reported Outcome Instruments for Use in Medical Device Evaluation[5]
- Patient Engagement in the Design and Conduct of Medical Device Clinical Studies[6]

To comply with those requirements and to optimize study results, IVD manufacturers should take special care to execute their patient recruitment, engagement, and retention strategies from a patient-centric lens, incorporating use of PRO data and other types of RWD into IVD studies. RWD can guide site selection and patient recruitment, demonstrate patient diversity, and augment the clinical evidence or provide context for IVD device performance by means of an external comparator. RWD can also provide contemporaneous controls in rare populations, monitor post-market safety and adverse events, and enable innovative clinical trial designs.

Validated PROs, a type of RWD, are used in clinical trials, providing unique information on the impact of a medical condition and its treatment from the patient's perspective. Therefore, PROs can be included as trial endpoints to ensure the impact of a trial intervention is comprehensively assessed. RWD represents device experiences outside the traditional study setting and provides valuable insights about device performance throughout the product's lifecycle.

Real-World Evidence (RWE), the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD, can be a stand-alone source of evidence for decision-making, multiple sources can be combined, or it can be used in conjunction with traditional clinical trial data.



Benefits and Barriers to Using Real-World Evidence

Benefits

RWE can complement trial findings by providing needed flexibility in study design, and by more clearly portraying how a device performs in real-world patient populations who may not be able to participate in traditional clinical research.

Benefits to using RWE include:

- Access to large datasets in a more timely and cost-effective manner
- Clinically rich insights and context into real-life experiences

Stakeholders across the healthcare ecosystem use this new knowledge to support decision-making and improve safety and effectiveness, and ultimately, patient outcomes.

Barriers

The use of RWE requires assessing, validating, and aggregating various, often disparate, sources of data available through routine clinical practice.

Specific challenges include:

- Selecting the best study protocol concept and design
- Defining the right endpoints and comparators
- Supporting patient recruitment, enrollment, and retention
- Generating high-quality clinical evidence
- Ensuring patient representation
- Reducing study costs
- Accelerating speed to market

Threats to the validity of RWD studies include unmeasured confounding, measurement error, missing data, model misspecification, selection bias, and fraud. Scholarly journals publish many observational studies, often without requiring the authors to report a thorough exploration of these threats to validity. Unless authors identify such threats and provide guidance about how they could bias study results, consumers of observational studies must trust the study authors to conduct the study with integrity and report it transparently.

Real-World Evidence to Support Regulatory Decisions

Still, the current state of RWE for regulatory assessment holds the promise of accelerating, streamlining, and optimizing regulatory decision-making and potentially reducing costs of bringing products to market.

The FDA assesses the relevance and reliability of the data sources and their specific elements. This assessment is then used to determine whether the RWD source(s) and the proposed analysis can generate evidence that's sufficiently robust for a regulatory purpose. In cases where RWE is derived from multiple RWD sources, the FDA evaluates each RWD source individually and in combination to determine the data's relevance and reliability.

The primary factors FDA considers for assessing the reliability of RWD include data accrual, data assurance and validity, and that the quality and integrity of the data is sufficient. In addition, generating evidence from RWD requires fit-for-purpose study design and data. In addition to data validity, regulatory decision makers require transparency in the reasoning that underlies study design and data source decisions.

Evaluating fit-for-purpose helps ensure the appropriateness and reliability of the data source selected to answer the specific research questions, and it enables regulators to confidently make decisions based on the evidence generated. Using a framework as a guideline can help researchers make the right choices to support acceptance of RWE by regulators. Medical device development requires a lifecycle approach, with product evaluations and modifications continuing even after a product initially reaches the market. RWE can be generated, and has the potential to be used, throughout a medical device's total product lifecycle because its use cases span the entire development spectrum.

Navigating Your Regulatory and Clinical Data Strategy

Navigating your regulatory strategy that includes nuanced clinical design features including sources of RWD and RWE is a complex process, requiring a clear roadmap. Incorporating RWD and RWE into your trial design will require regulatory, clinical, and data experts every step of the way.

About Halloran's Regulatory Affairs and Operations Services

Halloran's streamlined approach prioritizes precision in regulatory compliance, optimizing every facet from strategy development to operational execution. Dive into data-driven insights that empower informed decisions, offering a comprehensive understanding of regulatory intricacies. Trust in Halloran's reliability at every stage, where accuracy, compliance, and security ensure the integrity of your regulatory data.

About Halloran's Data Integrity and Compliance Services

Clinical development sponsors have incorporated more technology use over the years, resulting in sponsors investing in numerous clinical vendors and services as they move throughout their phases of development. The disparate systems often result in a complex data ecosystem, and the outsourcing often results in the generation and transfer of massive quantities of data.

Many sponsors do not have clarity around data integrity requirements and regulations, putting their product development programs at risk. Halloran consultants are subject matter experts prepared to define data strategies and ensure data is inspection ready, working in sync with Halloran's regulatory experts.

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References

1. M. Behnam, W. Cai, A. Dey, T. Gambell, V. Talwar. "COVID-19 and in vitro diagnostics: New market forces at play." McKinsey. December 11, 2020. www.mckinsey.com/industries/life-sciences/our-insights/covid-19-and-in-vitro-diagnostics-new-market-forces-at-play
2. K. Scott. "Where Does the IVD Market Go After the Coronavirus Testing Surge?" ADLM. December 1, 2022. www.myadlm.org/cln/articles/2022/december/where-does-the-ivd-market-go-after-the-coronavirus-testing-surge
3. FDA. "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices: Guidance for Industry and Food and Drug Administration Staff." August 31, 2017. https://www.fda.gov/media/99447/download
4. FDA. "Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims." December 2009. https://www.fda.gov/media/77832/download
5. FDA. "Principles for Selecting, Developing, Modifying, and Adapting Patient-Reported Outcome Instruments for Use in Medical Device Evaluation: Guidance for Industry and Food and Drug Administration Staff, and Other Stakeholders." January 26, 2022. https://www.fda.gov/media/141565/download
6. FDA. Patient Engagement in the Design and Conduct of Medical Device Clinical Studies: Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders." January 26, 2022. https://www.fda.gov/media/130917/download

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