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WHITEPAPER

Toward Full Decentralization of Evidence Generation with Medical Devices: Strategic Value and Applications

Dr. Ting-Yi Lin, MD, PhD
Medical Office,
Arcondis Group,
Basel, Switzerland

Arcondis

Giovanni Brusaferri
Medical Affairs,
mylife Diabetes Care AG,
Burgdorf, Switzerland

mylife DiabetesCare

Sandra Rosser
Medical Affairs,
mylife Diabetes Care AG,
Burgdorf, Switzerland

mylife DiabetesCare

Toward full decentralization of evidence generation with medical devices: strategic value and applications

A comparative analysis of hybrid and fully decentralized clinical studies with operational, regulatory and reimbursement evidence drawn from automated insulin delivery systems in Europe and the United States.

AUTHORS

Dr. Ting-Yi Lin, MD, PhD
Medical Office, Arcondis Group, Basel, Switzerland

Giovanni Brusaferri
Medical Affairs, mylife Diabetes Care AG, Burgdorf, Switzerland

Sandra Rosser
Medical Affairs, mylife Diabetes Care AG, Burgdorf, Switzerland

AUTHOR CONTRIBUTION

Dr. Ting-Yi Lin led the overall manuscript development and coordination. Giovanni Brusaferri and Sandra Rosser contributed specifically to the sections related to automated insulin delivery technologies.

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Executive Summary

The convergence of connected medical devices and digital health ecosystems has unlocked continuous streams of Real-World Data (RWD), fundamentally changing how clinical evidence is generated. To leverage these RWD streams in clinical research and evidence generation, manufacturers have been relying on hybrid clinical study designs combining remote and site-based activities. While this approach represents a significant improvement over traditional site-centric clinical studies, it still faces substantial operational bottlenecks. Specifically, hybrid designs remain constrained by the cost and logistical burdens of physical site onboarding and patient enrollment.

To evaluate the best path forward, this white paper presents a comparative analysis of clinical studies involving automated insulin delivery (AID) systems, examining the operational trade-offs between hybrid and fully decentralized clinical studies (DCS) models.

We examined the hypothetical mylife study – this illustrative model is not an active clinical study, but a representative operational scenario based on French post-market surveillance requirements as a representative example of a hybrid DCS (Info Box). By combining remote data capture with routine clinic visits, this model balances real-world validity with

INFO BOX: Fully decentralized vs hybrid decentralized studies with automated insulin delivery systems

The table below compares two models for a post-market observational study on automated insulin delivery systems in type 1 diabetes for conduction in a European country (France): a fully decentralized vs a hybrid decentralized study.

Comparison of two models for a post-market observational study:

Study	**Fully decentralized**	**Hybrid decentralized**
Objective	Post-market study for HAS/CEPS reimbursement	Post-market study for HAS/CEPS reimbursement
Design	Prospective, observational, no clinical sites	Prospective, observational, with clinical sites
Study subjects	1,000	240
Sites / Investigators	0	15 sites / 45 investigators
Recruitment Period	6 months (estimated)	12 months (estimated)
Follow-up Duration	12 months	12 months
Countries / Setting	France (remote)	France (clinical centers)
Cloud / Platform Compliance	HDS + ISO 27001	HDS + ISO 27001 + API integrations + safety portals

Despite a similar regulatory scope, decentralization in this estimation can cut costs by over €400,000 (≈ 57%). The savings are mainly achieved by eliminating site setup, investigator fees, on-site monitoring. The digital model also reduces recruitment time (6 months vs. 12 months) and improves scalability by enabling participation across broader geographic regions. This comparison highlights how decentralized setting can enhance both operational efficiency and data completeness in post-market research. Both approaches achieve regulatory-grade compliance (HDS + ISO 27001) and real-world data capture, but the digital model demonstrates how decentralized, cloud-based platforms can expand patient reach and data richness while reducing operational burden.

This cost-saving estimate is illustrative and based on a defined set of assumptions regarding study design, duration, recruitment, site requirements, monitoring activities, and unit costs. Actual costs and savings may vary depending on the specific study scope, geography, vendor arrangements, and operational requirements.

essential clinical oversight. This ensures robust safety monitoring. However, the operational burden remains high. Managing 15 clinical sites and their associated investigators within a pre-defined budget constrained enrollment to 240 participants and extended the recruitment timeline to 12 months. These limitations highlight the scalability challenges inherent to hybrid DCS models and underscore the need for more operationally efficient alternatives. A fully DCS operational model was then evaluated to assess whether regulatory-grade evidence generation could be achieved without dependence on physical investigational sites.

Fully DCS offer a scalable approach by eliminating the dependency on physical sites and enabling direct-to-patient recruitment through digital channels. Our analysis shows that in comparison with a hybrid model, a fully decentralized model has the potential to substantially reduce operational cost (savings are achieved primarily through the elimination of site setup fees, investigator payments, and on-site monitoring activities), the recruitment timeline (from 12 months to 6 months in the specific example), while potentially enabling substantially larger participant cohorts (from 240 to 1,000 participants in the specific example).

Within the field of AID, fully DCS with several hundreds of subjects have already been conducted in the US regulatory environment to address post-market surveillance requirements of three AID systems in type 1 diabetes: the Loop study [1], the CLIO study [2], and the ongoing Twiist-PS study [3]. These US examples demonstrate that decentralized models achieve high accessibility and inclusivity, reaching patients across wide geographic areas who might otherwise be excluded from traditional research.

However, replicating this fully remote success in Europe faces a critical hurdle regarding data reliability. Fully decentralized studies often rely on patients to self-report key safety outcomes. Without direct clinical assessment, this reliance introduces potential recall bias. Regulators such as the European Medicines Agency view these limitations with caution. To address regulatory concerns, technical frameworks are evolving to validate data without physical sites. Electronic health record integration allows for the automated validation of clinical outcomes, reducing the need for on-site verification. Advanced smartwatch algorithms are also increasingly used to detect safety signals proactively, such as arrhythmias or hypoglycemia, independent of patient recall. For the French market specifically, leveraging the National Health Data System provides a mechanism to cross-reference and confirm long-term safety data. This approach satisfies strict payer requirements for longitudinal follow-up.

Looking forward, adopting decentralized methodologies offers new opportunities for device development. By removing physical barriers, these models reveal how devices perform across diverse populations. This approach identifies unmet needs and usability challenges that traditional clinical studies often miss. It creates a continuous feedback loop, ensuring devices evolve to meet actual patient needs. While agentic AI is not yet a standard regulatory tool, it represents a future capability to automate these insights. Companies that invest in decentralized frameworks will be better positioned to demonstrate clinical value to payers, build trust with regulators, and improve patient outcomes in routine medical practice.

KEY TAKEAWAY

Companies that invest in decentralized frameworks will be better positioned to demonstrate clinical value to payers, build trust with regulators, and improve patient outcomes in routine medical practice.

Introduction

Real-World Evidence (RWE) has become a central component of medical device evaluation across the product lifecycle. The FDA defines RWE as clinical evidence regarding the usage, potential benefits, or risks of a medical product, derived from the analysis of Real-World Data (RWD) [4,5]. Essentially, RWD encompasses the information collected from patients during everyday clinical care and routine device use. These data sources may include electronic health records (EHRs), patient-reported outcomes (PROs), administrative claims, registries, connected medical devices (e.g., wearable monitors and implant logs), and other digital health streams[6].

Connected wearable devices (e.g., automated insulin delivery (AID) systems, pacemakers, continuous positive airway pressure machines, or home dialysis machines) generate continuous data streams of RWD related to device performance and/or patient outcomes. These data streams provide an opportunity to evaluate a device's effectiveness under routine conditions at an unprecedented scale.

For example, devices used for diabetes management, in particular AID systems used by people with type 1 diabetes (Figure 1), demonstrate this potential particularly well, as they generate extensive data on glucose control, device adherence, and user interaction patterns [7,8]. Modern analytics transform this RWD into practical RWE that demonstrates real-world effectiveness, reveals long-term safety trends, and supports personalized disease management strategies [4,9,10]. This interconnected ecosystem of devices, data, and analytics produces broad RWD that, when analyzed, generates valuable RWE for regulators, payers, clinicians, and manufacturers [11].

RWE in the MedTech industry offers a fresh perspective on how routine clinical use can be leveraged to further improve device safety, effectiveness, and value beyond the limits of controlled studies. In the case of AID systems, specifically, RWE provides a realistic look at performance "in the wild" (i.e., actual patient environments rather than research settings). This delivers insights that support regulatory decisions and market access, drive improvements in devices, and, more importantly, benefit patient outcomes. The convergence of regulatory evolution, technological advancement, and the demands for demonstrating value from healthcare systems has positioned RWE as a core capability for medical device manufacturers [11,12]. Companies that harness the power of RWD will accelerate market access, optimize reimbursement, and continuously improve their products based on actual patient outcomes.

However, translating RWD into regulatory- and payer-acceptable evidence remains challenging because RWD often lacks the level of control and standardization associated with traditional clinical studies. As a result, hybrid Decentralized clinical studies (DCS), rather than fully DCS models, currently represent the dominant operational approach for generating regulatory-grade RWE in Europe.

FIGURE 1. Example of an interconnected automated insulin delivery system: myLoop plus Glooko diabetes management platform [13,14]

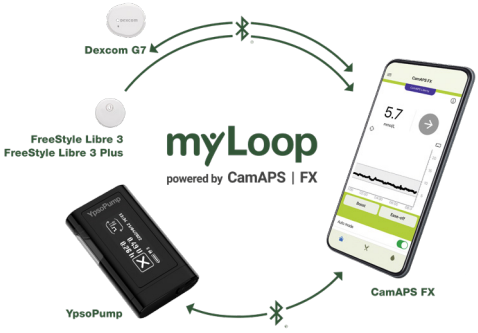
myLoop
mylife Diabetes Care

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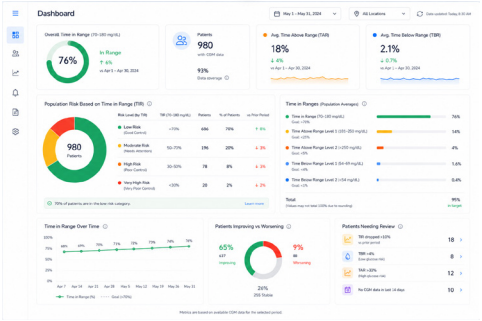
Glooko®
A diabetes management platform, which connects and aggregates data from difference AID systems

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Example of a clinical dashboard



glooko®
BETTER TOGETHER





Regulatory and Payer Landscape

REGULATORY ACCEPTANCE OF RWE

Global regulators are increasingly embracing RWE for medical devices, recognizing its value in providing comprehensive safety and effectiveness data throughout a device's lifecycle. In the United States, the FDA's 2017 guidance (as well as the 2023 extension) encourages using fit-for-purpose RWD sources (e.g., registries, EHRs, claims databases, and digital health data) to generate evidence for device regulatory decisions [15,16]. The FDA acknowledges that while traditional study data remain important for establishing initial safety and efficacy, there is a wealth of RWD covering medical device experience from routine clinical care that can answer critical regulatory questions. These data provide insights into device performance across diverse patient populations, real-world usage patterns, and long-term outcomes that traditional studies cannot feasibly capture.

Comprehensive systems and infrastructure are essential for leveraging this data effectively. The National Evaluation System for health Technology (NEST) , a public-private collaboration co-funded by the FDA, serves as a medical device RWE marketplace, giving manufacturers streamlined access to high-quality and validated RWD sources [17]. NEST supports the sustainable generation and use of reliable and cost-effective RWE throughout the total product lifecycle. The platform connects device innovators with experienced researchers and data partners while facilitating standardized data collection through common protocols. This approach reduces the risk of using RWD in regulatory filings by improving evidence confidence and making medical device evaluation more predictable. According to the FDA, when leveraged correctly, such coordinated networks can significantly reduce the time and cost of evidence generation for both initial approvals and post-market studies, while maintaining high evidentiary standards [17,18].



In the European Union, the Medical Device Regulation (MDR) also recognizes and integrates RWD into regulatory frameworks [19,20]. EU guidance specifies that data collected through post-market activities (i.e., patient registries, EHRs, and clinical use during routine care) constitute valuable forms of RWD that can generate regulatory-grade RWE. Manufacturers must provide clear justification for their use of RWD in clinical evaluations, including detailed methodology, data quality assessments, and statistical analysis plans. For orphan devices or high-risk implantable devices, regulators explicitly state that RWE can help detect rare complications, understand performance across diverse patient groups, and identify device-related risks that may only emerge after extended use [21].

In practice, EU implementation has shifted from expectation to strict enforcement. Manufacturers must align post-market surveillance processes with evolving EUDAMED implementation requirements, specifically EUDAMED modules (v2.0, 2025). This requires ensuring robust Unique Device Identification linkage and Post-Market Clinical Follow-up (PMCF)

traceability to meet transparency standards. These requirements are heavily emphasized at the national level. For example, France's ANSM 2025 guidance mandates rigorous traceability for implantable devices. This reinforces that systematic RWD analysis is now a non-negotiable part of the device's continuous lifecycle assessment [22].

Other major regulatory bodies, including Health Canada [23], Japan's Pharmaceuticals and Medical Devices Agency [24], and Australia's Therapeutic Goods Administration [25], similarly show growing interest in RWE for device regulation. These agencies are developing their own frameworks and guidance documents for incorporating RWE into regulatory decision-making. In all cases, the emphasis remains on data quality, methodological rigor, and transparency. Agencies consistently advise that only RWD meeting stringent standards for accuracy, completeness, and relevance can support regulatory submissions. RWE is acceptable when the underlying RWD is of sufficient quality to answer the specific regulatory question at hand. New FDA draft guidance [16], along with evolving industry standards, are further clarifying best practices for data collection (i.e., common data models, statistical methods, and bias mitigation strategies). These developments ensure that RWE can be trusted for regulatory decisions. Overall, regulators view RWE as a powerful tool to complement traditional studies, enabling more efficient approval processes, stronger post-market safety monitoring, and better understanding of real-world device performance.



PAYER AND REIMBURSEMENT

Health insurers, health technology assessment (HTA) bodies, and other payers also increasingly value RWE for medical devices and recognize its ability to demonstrate value in real-world healthcare settings. Payers and HTA bodies (e.g., NICE in the UK, IQWiG in Germany, CADTH in Canada, and Haute Autorité de Santé [HAS] in France) demand robust evidence of value and safety, and RWE is becoming integral in satisfying these requirements. Recent studies show that payers worldwide are systematically incorporating RWE into their coverage and pricing decisions, using it to assess clinical and cost-effectiveness and budget impact in their specific patient populations [26–28]. RWE can reduce the uncertainties payers face when a new device enters the market, particularly when study data are limited in scope or duration.

HTA bodies increasingly accept well-designed RWE studies as part of their assessment frameworks. It is now common to see FDA advisory panels and HTA bodies evaluations referencing RWE analyses in their deliberations [29]. Credible RWE strengthens reimbursement dossiers by quantifying outcomes in routine care, meeting payer demands for demonstrable real-world effectiveness. RWE on device-related outcomes (i.e., hospital readmission rates and healthcare utilization patterns) may be used in initial coverage reviews, value-based pricing negotiations, or post-launch coverage-with-evidence-development arrangements where initial coverage is granted contingent on collecting additional RWE [30].

At the same time, payers maintain high standards and stress the need for methodological rigor in RWE studies. They expect RWE studies to meet standards of validity, reliability, and transparency comparable to traditional clinical evidence. According to recent reviews, payers remain appropriately cautious about RWE quality, with concerns about potential data gaps, selection bias, confounding factors, or inadequate methodology [26,31,32]. Many payers currently use RWE primarily as supplementary evidence alongside randomized study data rather than as standalone proof of effectiveness. Nonetheless, as RWE frameworks continue to mature through initiatives (e.g., AMCP guidelines [33], NICE's RWE framework [34]), and as more high-quality RWE studies are published, payers increasingly recognize RWE as an essential component of the comprehensive

evidence package for new devices. This evolution is driving greater standardization in RWE methods and reporting, making it easier for manufacturers to generate evidence that meets payer expectations across multiple markets [35].

SPECIFIC REIMBURSEMENT FRAMEWORKS IN EUROPE

In France, HAS and its medical device committee (CNEDiMTS) employ a method-agnostic evaluation framework. While prioritizing internal validity and bias control, HAS increasingly requires evidence collected under real-world conditions from representative populations. The HAS methodological guide explicitly identifies routine clinical practice and daily device use as valid inputs for clinical benefit assessments [36]. Valid RWD sources, such as the National Health Data System (Health Data Hub), can be actively mobilized alongside connected device data [37]. A prime example is the SFDT1 study, a 10-year prospective French cohort leveraging connected continuous glucose monitor (CGM), electronic ePROs, and the Health Data Hub to track longitudinal outcomes in people with type 1 diabetes [38].

For certain high-value devices, HAS now requires post-market evidence on the exhaustive patient population (all users) rather than just a sample. For example, regarding the myLoop powered by CamAPS FX AID system, regulators request comprehensive follow-up data to confirm real-world effectiveness [39]. Decentralized study designs structurally align with these HAS expectations. By capturing protocol-driven data in the patient's actual care environment, they reduce the ecological validity gap inherent in traditional site-based studies. Broadening enrollment beyond standard investigator sites also improves population representativeness, a key criterion for HAS's external validity assessment.

France has built the regulatory infrastructure to support this convergence. Following a 2024 pilot phase [40], an April 2025 FAQ issued by the Directorate General for Health (DGS), the ANSM, and the CNIL officially confirmed that a participant's home qualifies as a research site [41]. Furthermore, patient follow-up via telemedicine and remote data collection through connected devices are legally admissible. Therefore, decentralized RWE is the most practical way to collect compliant data on the entire user base to secure and maintain reimbursement.

In Germany, the Digital Healthcare Act (Digitale–Versorgung–Gesetz or DVG) created the "DiGA Fast Track" for digital health applications (only applicable to EU risk class I or IIa medical devices). This allows devices to be temporarily reimbursed based on safety and function, with permanent reimbursement granted only after RWE demonstrates positive care effects within the first year [42]. This model highlights the need to harmonize assessment and reimbursement of digital medical devices across the EU through mutual learning.

To satisfy payer requirements, RWE must be integrated into evidence generation strategies from the earliest stages of product development. The Medical Device Innovation Consortium (MDIC) advises that manufacturers adopt a comprehensive, integrated RWE strategy that spans research and development, regulatory affairs, and commercial functions [43]. This coordinated approach ensures that data collection is aligned with both regulatory and payer needs from the outset. Device companies should engage regulators and payers early in the development process. Submitting RWE through ongoing device registries or connected device platforms can strengthen both regulatory submissions and payer discussions. Properly designed RWE studies, with pre-specified endpoints and robust methodology, can yield more reliable and persuasive evidence than fragmented, post-hoc approaches. This ultimately improves patient outcomes while accelerating market access and adoption.



Decentralized Clinical Studies: from hybrid to full decentralization

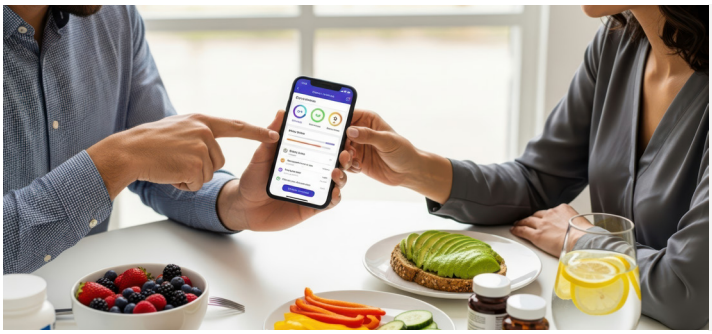
CURRENT TREND

DCS, the operational methodology used to collect/manage the clinical data, represents a structural evolution on how clinical evidence is generated. This operational methodology for collecting and managing clinical data moves key study activities from traditional clinical sites to participants' homes. By leveraging RWD from wearable, telehealth consultations, home health services, electronic consent, and direct delivery of devices or medicines, DCS expand access to broader and more representative populations while making study participation far less burdensome [44,45]. This shift can also be valuable for people that traditional research might overlook (e.g., people in rural areas, patients with mobility challenges).

DCS are transforming how we study medical devices across different therapeutic areas [46]. The flexibility inherent in decentralized approaches works especially well for wearable medical devices that continuously generate RWD related to clinical outcomes of medical device performance. For example, patients can receive cardiac rhythm monitors at home and transmit ECG data remotely. Similarly, digital spirometers capture lung function data in the daily environments of asthma or COPD patients [47]. Sleep apnea devices, blood pressure monitors, and even post-surgical monitoring systems can all be studied through decentralized methods.



However, decentralization is not an absolute requirement. It exists along a range from site-based studies augmented with RWD to fully remote models (Table 1). By design, DCS minimize what we ask of participants while maximizing enrollment potential. These flexible models help studies reach diverse populations, sustain engagement, and reduce missing data. Simultaneously, they generate data to inform future RWE analyses. Specific DCS elements deliver trackable and measurable improvements:



Digital Data Collection: Apps and wearables enable real-time data capture. Sponsors must use wearables validated or cleared for clinical use. Data protection remains a primary challenge, and sponsors must verify that data flows comply with local regulations (e.g., GDPR) before deployment.



Telemedicine Consultations: Virtual assessments complement home nursing visits and device training, reduce travel expenses, and improve participation rates. Participant retention rates improved and missed visits decreased with telemedicine, even though there are technical challenges and regulatory variations across different countries to overcome.



Direct-to-Participant (DtP) Device Shipment: Delivering investigational devices straight to participants' homes reduces travel requirements. This increases convenience for elderly participants with limited mobility or multiple health conditions.

Decentralized approaches can speed up study enrollment and data collection while building RWE infrastructure. As noted by the Clinical Trials Transformation Initiative, digitalizing studies allows for more efficient evidence generation [48]. Digital recruitment through patient registries and EHRs can identify eligible participants across much broader geographic areas than traditional site-based recruitment, provided that the registries are correctly set up to allow patient identification and contact in compliance with data privacy laws. Automated data captured from connected devices (e.g., insulin pumps, cardiac monitors) can also reduce the burden of manual data entry. Additionally, the same data collection systems established for DCS can continue generating RWD after study completion, which helps transition into post-market RWE studies. Hybrid designs offer additional flexibility: a study might begin with in-person training for complex devices, then transition to remote monitoring with continuous RWD collection that persists beyond the study follow-up period.

Nevertheless, industry experience shows considerable variation: digital recruitment in the US proved relatively straightforward, but European deployment required country-specific approaches to address varying privacy requirements. Success in Europe often depends on local ethics committees and varying national privacy requirements, which can lead to higher screening failure rates if not managed with experienced local vendors.

Most importantly, the regulators are increasingly recognizing DCS as part of the future of clinical research because they generate evidence that more closely reflects real-world use patterns [49].

Table 1. Spectrum of decentralization of clinical studies: from traditional site-centric studies to hybrid and fully decentralized

Study Feature	Traditional site-centric	Hybrid decentralized	Fully decentralized	Enabling Tools to move from hybrid to full decentralization
Study Setting	All visits occur at physical investigation sites	Critical visits (e.g., device implant / training) at site + follow-ups remote	No physical site visits	Telehealth platforms, Home Health Nursing networks
Screening & Enrollment	Paper-based screening and consent at the clinic	Online pre-screening. Final eligibility/consent at site (or via eConsent)	Fully digital recruitment, eligibility verification, and eConsent	Web-based ID verification API, eConsent with video comprehension checks
Device Logistics & Training	Device dispensed at site. In-person training by Investigator	DtP or picked up. Training via video or site visit	DtP shipment. Self-training via app or virtual coach	DtP logistics platforms, Learning Management Systems for patient training
Data Collection	Data transcribed from paper source to electronic database by site staff	Mix of site-entered data and patient remote uploads	Direct digital capture from devices/apps/wearables. No manual transcription	eCOA/ePRO apps, API integration with connected devices (e.g., GlucoTab, Fitbit)
Patient Monitoring	Scheduled in-person assessments	In-person safety checks + remote vital sign monitoring	Continuous or frequency-based remote monitoring with alert thresholds	Agentic AI for safety signals, Cloud-based remote monitoring dashboards
Safety & Adverse Events	Detected during site visits or patient phone calls	Real-time reporting via app. Adjudication based on hybrid data.	Auto-detection of safety signals (e.g., hypoglycemia, arrhythmia) via sensors	Algorithms for adverse event detection, secure messaging apps
Investigator Oversight	On-site supervision with 100% Source data verification.	Risk-based monitoring + remote review of central data	Centralized Principal Investigator + remote monitoring of data streams	Risk-Based Quality Management tools, Centralized statistical monitoring
Source Data Verification (SDV)	100% on-site SDV against paper and EHR source	Risk-based SDV with remote access to eSource + targeted on-site visits	Centralized, risk-based monitoring with limited or no traditional SDV	eSource systems, RBQM platforms, remote EHR access, audit trails
Regulatory Compliance & Inspection Readiness	Physical TMF at site, on-site inspections	Hybrid TMF with remote inspection readiness	Fully digital TMF, remote inspections	eTMF systems, validated document management, inspection portals
Data Quality Controls	Manual checks, query-based cleaning	Automated checks + manual review	Real-time validation and anomaly detection	Real-time edit checks, statistical monitoring, AI-driven data quality tools
Patient Engagement & Retention	Site-driven reminders, passive participation	Mixed site + digital engagement	Continuous digital engagement, self-management	Mobile apps, push notifications, chatbots, digital coaching
Privacy & Identity Verification	In-person identity verification	In-person + digital verification	Fully remote identity verification	ID verification APIs, secure authentication, GDPR-compliant platforms
Role of Site & Investigator	Site as primary execution hub	Site as clinical anchor + remote support	Site as supervisory or centralized PI function	Tele-investigator models, centralized oversight platforms
Participant Support	Site contact during visits	Site + remote helpdesk	24/7 remote support, virtual assistance	Helpdesk platforms, secure messaging, AI-based triage

EXAMPLE 01

HYBRID DCS WITH AN AID SYSTEM

The hypothetical mylife clinical study

240
PARTICIPANTS
(120 ADULTS, 120 PEDIATRIC)

15
CLINICAL SITES
ACROSS FRANCE

12 month
FOLLOW-UP PERIOD

The myLoop powered by CamAPS FX AID system is CE marked and approved for reimbursement in France. To maintain this reimbursement status, mylife Diabetes Care must conduct a comprehensive, prospective clinical study on patients using the system in France. The goal is to generate clinical data regarding glycemic control benefits, quality of life, complications, and the utilization rate of the system under routine care conditions. The following hypothetical study model illustrates a representative hybrid PMCF design aligned with French reimbursement requirements.

The hypothetical mylife study is a hybrid decentralized, prospective, post-market observational study. It evaluates the above-mentioned AID system in people with type 1 diabetes (PwT1D) under routine care conditions. The system combines the mylife YpsoPump insulin pump, the mylife CamAPS FX mobile application, and a compatible CGM sensor. Therapy management occurs directly via the smartphone of the PwT1D. The user synchronizes data cloud-to-cloud with the Glooko intelligent connected care platform to share information with the clinic.

The hypothetical mylife study includes 240 participants (120 adults, 120 pediatric) **across 15 clinical sites** over a 12 month-follow-up period, integrating remote digital data capture with site-based routine care visits, consistent with a hybrid DCS design. Device-generated RWD, such as insulin delivery, CGM metrics, and system usage, are captured digitally via cloud-to-cloud synchronization with the Glooko platform. This allows for continuous remote data aggregation and review. Clinical assessments (e.g., HbA1c) and safety oversight are performed during standard-of-care clinic visits, without protocol-mandated study visits beyond routine practice.

Patient-reported outcomes are collected using **validated digital questionnaires**, including the DTSQs/DTSQc, WHO-5, and PAID scales, enabling assessment of treatment satisfaction, well-being, and diabetes distress. By combining remotely collected device data with site-based clinical measures and PROs, the study generates regulatory-grade real-world evidence on safety, effectiveness, and quality of life, in compliance with EU MDR and GDPR, while supporting payer requirements for continued reimbursement. Safety events and specific metabolic control measures (e.g., HbA1c) are collected on site as part of routine clinical visit.

PROS OF THE DESIGN

+ **Balanced real-world validity and clinical oversight**
  This design combines continuous remote data capture with routine clinic visits. It ensures real-world generalizability while maintaining necessary clinical validation and safety oversight.
+ **Reduced participant and site burden**
  Embedding data collection into existing care pathways limits additional study visits. This improves feasibility and retention compared with fully site-based designs.
+ **Rich, multi-source data integration**
  Cloud-based aggregation of pump data, CGM metrics, app usage, and PROs enables a comprehensive evaluation of physiological outcomes and patient experience.
+ **Regulatory and payer alignment**
  Supports EU MDR post-market surveillance requirements while generating outcomes relevant for reimbursement renewal and HTA evaluation.
+ **Scalable digital infrastructure**
  Demonstrates how connected device ecosystems (AID + CGM + data platforms) can support long-term lifecycle evidence generation and continuous product improvement.

CONS OF THE DESIGN

- **Operational complexity and site management requirements**
  Hybrid DCS models require coordination between digital platforms, clinical sites, and data governance processes. The study still requires site enrollment and coordination across multiple clinics. It also necessitates investigator engagement and local study management.

Conclusion

This hybrid DCS design illustrates a key operational limitation: while remote data capture enables continuous and scalable collection of device-generated outcomes, regulatory-grade evidence in the European context still depends on validated clinical measurements and verifiable safety reporting. The inclusion of site-based assessments for endpoints such as HbA1c and adverse events ensures traceability. However, this reliance on clinical sites introduces operational constraints that limit scalability and increase cost. As a result, hybrid DCS designs currently represent a necessary compromise between evidentiary rigor and operational efficiency.



EXAMPLE

FULLY DECENTRALIZED STUDIES WITH AID SYSTEMS

02 The Loop study[1], CLIO study[2] & the Twiist-PS study[3]

The Loop study

An earlier proof-of-concept for fully decentralized diabetes research was demonstrated in the prospective observational study of the open-source Loop AID system in the US. The study enrolled **558 participants** (adults and children with type 1 diabetes) across the US and was conducted entirely remotely, without clinic visits. Participants provided data directly from their devices through continuous cloud-based uploads, while adverse events and device issues were collected through automated digital prompts and participant reporting. The study demonstrated that fully remote evidence generation using connected diabetes technologies was feasible and could produce clinically meaningful real-world outcomes.

The CLIO study

The CLIO study was a fully decentralized, prospective, post-market observational study conducted entirely remotely in the US over 12 months. The study digitally recruited **over 3,000 participants** with type 1 diabetes (diagnosed for at least 6 years) who were initiating the t:slim X2 insulin pump with Control-IQ technology. Participants provided electronic informed consent and completed all study activities without in-person visits.

Researchers collected safety data, specifically severe hypoglycemia and diabetic ketoacidosis, via monthly online surveys. They supplemented this with remote monitoring of manufacturer support logs and centralized remote adjudication of events. Glycemic outcomes came from remote uploads of device and CGM data. This process was often automated through a smartphone app. Validated digital questionnaires captured PROs quarterly. Clinical care, training, and device setup occurred independently of the study. This approach reflected real-world practice rather than protocol-driven visits.

The Twiist-PS study

The Twiist-PS is a prospective, observational post-market surveillance study in the US involving approximately **1,900 participants** aged 6+ with type 1 diabetes who already use the twiist™ AID system. Over 12 months, participants continue everyday use with no protocol-mandated in-person visits, as data collection relies on routine device use and participant reporting rather than site-based clinical assessments.

The study gathers safety data, such as severe hypoglycemia events, through monthly participant surveys. Researchers also review support or device data as available and contact participants for clarification if needed. Device effectiveness and usage patterns come from remote twiist system data and participant-provided information. Participants agree to share data from the twiist system and associated records. They also agree to be contacted for event clarification or to provide medical records if hospitalizations occur. The study is currently ongoing (ClinicalTrials.gov: NCT07356089).

PROS OF THE FULLY DECENTRALIZED DESIGN

+ **High accessibility and inclusivity**
This design enables participation across wide geographic areas without requiring in-person visits. It reduces barriers related to travel, mobility, or health-system access. This is particularly effective for AID users who already engage digitally with their therapy.
+ **Strong real-world generalizability**
Minimal protocol interference allows data to reflect routine clinical practice, everyday device use, and real-world training pathways rather than idealized trial conditions, strengthening external validity.
+ **Scalability and rapid evidence generation**
Large national enrollment **(over 1,000 people with diabetes)** and remote follow-up support faster study completion and larger sample sizes than traditional site-based post-market studies.
+ **Lower operational and participant burden**
Eliminates the need for physical sites, frequent clinic visits, and travel, reducing cost and burden for sponsors, sites, and participants.
+ **Continuous digital data capture**
Remote device and CGM uploads enable frequent and longitudinal collection of safety and effectiveness data. This is often automated through connected platforms or mobile apps.

NOTE: *the above studies were conducted in a US regulatory environment with different operational and data-verification expectations compared with Europe.*

CONS OF THE FULLY DECENTRALIZED DESIGN

- **Reliance on self-reported adverse events**
Key safety outcomes (e.g., severe hypoglycemia, diabetic ketoacidosis) are collected via participant surveys rather than direct clinical assessment or claims data. This introduces potential recall or reporting bias despite verification procedures.
- **Potential data gaps, bias, or inaccuracies in participant-reported data**
Variability in survey completion or interpretation of events can result in missing or inconsistent data in participant-reported information.
- **Variability in training and clinical oversight**
Because training, follow-up, and clinical care occur outside the study protocol, heterogeneity in user education and support may increase outcome variability.



REGULATORY FRAMEWORK

Regulatory agencies now provide comprehensive guidance for DCS and RWE in drugs and devices [50] (Table 2).

United States: FDA Guidance

In the United States, the FDA's 2024 guidance on "Decentralized Elements" formally defines DCS and permits fully remote wstudies for suitable products [51]. There is no blanket legal prohibition against fully decentralized studies; a study can be conducted entirely without a traditional physical hospital or clinical site. The guidance acknowledges that decentralized elements can be incorporated into traditional studies (i.e., creating hybrid models) or go fully decentralized where no physical study site exists. Still, DCS must maintain the same standards for participant safety, rights, and welfare as traditional study and require approval from the Institutional Review Board. If the study incorporates investigational device components, FDA approval of an Investigational Device Exemption may also be necessary depending on the specific study design.

The feasibility of this fully remote framework was demonstrated by the prospective observational study of the Loop open-source AID system in 2021 [1]. Participants provided electronic consent through a study website, and their system data was continuously streamed to a central data aggregator. Device issues and adverse events were self-reported through weekly automated text and email prompts, with no clinic visits required. As detailed in the CLIO study (see Example 2), this site-less approach has since matured to support large, digitally recruited cohorts, successfully collecting robust safety and glycemic data remotely.

While fully decentralized studies expand participant access, they introduce distinct challenges around data integrity. Maintaining confidence in self-reported safety data submitted through online surveys is inherently difficult. To ensure data reliability and reduce potential bias, sponsors must establish robust oversight mechanisms. Assigning a Medical Monitor to conduct periodic reviews of reported information is strongly recommended. Sponsors should also deploy a small, trained team responsible for direct communication with participants, with follow-up by email, text, or telephone whenever self-reported data is ambiguous or incomplete. These active monitoring strategies help ensure that DCS uphold the same high standards for participant safety, rights, and welfare as traditional studies.

European Union: EMA, HMA, and EC Recommendations

In Europe, the EMA, the Heads of Medicines Agencies (HMA), and the European Commission (EC) have published joint recommendations on decentralized clinical studies. These joint recommendations emphasize participant safety and consistent oversight, regardless of whether activities occur on-site or remotely [52]. The European framework treats DCS elements as tools to deploy appropriately rather than replacements for traditional site-based studies. The recommendation paper details best practices for implementing specific DCS elements (i.e., telemedicine, direct-to-participant device delivery, electronic consent, mobile healthcare providers, digital health technologies, and digital recruitment) while acknowledging variation in national requirements across EU countries.

This national variation creates challenges for multinational studies. While FDA allows electronic consent remotely with appropriate safeguards, many EU countries impose stricter requirements [53]. Here are a few examples:

- **Germany:** Imposes technical requirements that may restrict telemedicine use.
- **France:** Mandates careful privacy management, including restrictions on using participants' email addresses in certain contexts.
- **Sweden:** Requires video interaction during remote electronic consent processes.
- **Denmark:** Allows electronic consent only with active participant dialogue, which rules out pre-recorded video alone.

Multinational studies must navigate varying regulatory frameworks that create significant operational challenges. There are often uncertainties about which DCS elements are permissible across different jurisdictions, difficulties in obtaining timely access to country-specific requirements, and the need to ensure compliance with diverse data privacy regulations (e.g., the General Data Protection Regulation in Europe) for digital DCS components. It must be taken into consideration that the absence of harmonized guidelines can lead organizations to adopt conservative study designs that exclude potentially beneficial decentralized elements to avoid regulatory ambiguity, or to allocate substantial resources to manage differing national requirements.

TABLE 2: Comparison between FDA and EMA guidance on decentralized studies.

Category	FDA guidance	EMA guidance
Study Design Consider population, disease, comorbidities, device type, safety profile, complexity of procedures.	• Sponsor-led assessment with risk-based monitoring	• Formal assessment with critical-to-quality factors documented
Informed Consent Ensure voluntary, informed consent complying with applicable regulations.	• Central IRB recommended • Flexible remote consent	• Face-to-face preferred • Vulnerability-based approach • Real-time video for remote
Service Providers Permit telehealth visits when appropriate with privacy measures for in-home/ telehealth visits.	• Study personnel may be sent to participants' homes • Local HCPs perform routine activities not unique to research	• Written agreements required • Formal due diligence mandatory
Device Delivery & Administration Conduct risk assessment considering route of administration, observation period, emergency plans, drug preparation, stability, storage, and shipping robustness.	• Focus on accountability and disposition documentation	• Authorize vendors or qualified GDP service providers • Establish monitoring, return, and destruction procedures
Investigator role Maintain sponsor and investigator responsibilities and ensure proper coordination and record keeping of contracted services.	• Supervision and delegation authority	• Ultimate responsibility; must approve service providers
Data Integrity Address potential variability from multiple data collection sources. Require an overview of data flow from creation to final storage with multiple source coordination.	• Consistency through training/ supervision	• Equivalence to on-site studies required, prospective limitation discussion • Specify digital literacy discrimination prevention

METHODOLOGIES AND DATA SOURCES

One primary challenge in DCS is the complexity of collecting, securing, and managing data. Ensuring data integrity and consistency across various sources requires robust technical infrastructure and quality assurance.

Data Integration: Making RWD reliable requires standardization and cleaning of data from diverse devices and systems. Sources can be heterogeneous, ranging from EHRs and insurance claims to wearable device streams and PROs. Adopting common data models (e.g., FHIR standards) and implementing validation pipelines help maintain consistency and quality. Advanced platforms continuously aggregate RWD, detect anomalies, and harmonize formats, which is essential for linking multiple data streams to understand device performance across diverse care settings.

Study Designs and Analytical Methods: RWE studies employ different designs like retrospective cohort analyses, prospective observational studies, case-control setups, and pragmatic trials. Since these approaches often lack randomization, analysts must apply statistical methods (e.g., propensity score matching, instrumental variable analysis, and time-to-event analysis) to adjust for confounding factors. Transparency through pre-specified protocols and statistical analysis plans is essential. Both the FDA and EMA stress early engagement regarding these methods. Purely observational device studies often do not require an Investigational Device Exemption, which streamlines the research process.

Connected Devices: Modern medical devices generate continuous, objective data streams that serve as primary RWD sources (e.g., insulin pumps record basal rates; continuous positive airway pressure machines log usage hours and respiratory events). Researchers extract these device-generated data via APIs or cloud platforms to measure treatment effectiveness and patient adherence directly.

Electronic Health Records: Clinical databases capture patient demographics, diagnoses, lab results, and procedures. Claims data add healthcare utilization and costs. Linking device data with EHRs correlates daily device use directly to clinical outcomes. For example, investigators can integrate hospital EHRs on infection rates with orthopedic implant data to assess long-term real-world safety.

Registries and Cohorts: Disease or device registries systematically collect structured, longitudinal data on device users. Such registries can offer high quality RWE sources, as they often aim to enroll all users within a region or healthcare system. High-quality registries (e.g., the Diabetes Collaborative Registry for diabetes management or the National Cardiovascular Data Registry for cardiac devices) aim to enroll all users within a region to capture adverse events and long-term outcomes. When national registries are unavailable, manufacturers can create product-specific registries to fulfill PMCF requirements.

Patient-Reported Data: Mobile apps and digital surveys gather PROs on quality of life, symptom burden, functional status, and treatment satisfaction. This patient-generated data adds critical real-world context. It makes studies more comprehensive by capturing the outcomes that matter most to patients beyond purely clinical measurements.

Social Determinants and Genomics: While still developing, data on social determinants of health from public records or community surveys could enhance RWE by adjusting for socioeconomic factors that influence device access and outcomes. Similarly, genomic data can help identify patients who respond differently to specific therapies. Incorporating these emerging data sources helps explain variations in real-world effectiveness across diverse patient populations.

DATA QUALITY AND INTEROPERABILITY

Systematic approaches are necessary to ensure high-quality RWD. The FDA recommends using standardized data dictionaries, consistent definitions, and validated algorithms to identify outcomes [51]. In practice, this involves aligning clinical metrics to common formats and ensuring device logs are interpreted uniformly across systems. For example, it is important to define "device failure" consistently across products from different manufacturers, standardize pain scores across studies, and harmonize definitions of clinical improvement.

Interoperability standards (e.g., HL7 FHIR or IEEE 11073) enable the exchange of device data between systems. FHIR implementation guides cover various device types, from glucose monitors to ventilators. Standardized coding systems, including ICD-10, CPT, and LOINC, ensure consistency for insurance claims and EHRs. When merging data from multiple sources, accurate patient matching using secure, de-identified keys and proper time alignment of clinical events are critical for maintaining data integrity.





Integration with advanced Artificial Intelligence

Advanced artificial intelligence (AI) is transforming how we analyze and manage RWD. Traditional machine learning algorithms can process continuous data streams from various devices to identify trends, predict outcomes, and detect safety signals. More recently, agentic AI, which refers to autonomous systems capable of making decisions and performing tasks independently, has expanded the scope of data analytics. Unlike basic generative AI that only responds to user prompts, agentic AI can act on data in real time.

These capabilities apply across therapeutic areas (e.g., diabetes management, post-surgical recovery, respiratory monitoring). Building on these platforms, agentic AI could further enhance study efficiency. For example, in a study for an AID system, an agentic AI could continuously monitor the "Time in Auto Mode." If the system detects that a participant frequently exits the closed-loop control due to specific alarms or connection failures, the agent could autonomously intervene by pushing a targeted troubleshooting guide to the patient's app and simultaneously flagging the site nurse to review the device settings. Some industry opinion pieces suggest that agentic systems could free up more than 50% of staff capacity in MedTech operations, allowing researchers to focus on clinical strategy and patient care [54].



AI IN DATA CURATION AND ANALYSIS

AI tools can help automate the cleaning and integration of complex RWD sources, which is especially important when data comes from different device types and formats. Natural language processing (NLP), for example, can extract relevant details from unstructured text in EHRs (e.g., clinical notes or patient reports). These analyses can uncover information about device-related complications, PROs, or clinician observations of device performance. NLP can identify descriptions of wound healing near orthopedic implants, breathing issues related to respiratory devices, or skin irritation linked to wearable sensors.

Time-series analysis algorithms can also detect subtle patterns in continuous data streams. In diabetes care, these algorithms analyze continuous glucose data to predict hypoglycemic events hours before they occur, identify post-meal glucose excursions that indicate incorrect carbohydrate ratios, and detect dawn phenomenon patterns. In sleep medicine, these algorithms link CPAP usage patterns directly with daytime functioning. Manufacturers are increasingly using these analyses to group patients based on response patterns, identify outliers (e.g., inconsistent device use or abnormal wear), and prepare optimized datasets for regulatory submissions. These insights help determine which patients benefit most from a device and where iterative improvements are needed.

PREDICTIVE MODELING AND PERSONALIZATION

Combining large-scale RWD with machine learning makes it possible to develop robust predictive models across many device categories. These models can uncover patterns that link patient behavior or physiological signals with clinical outcomes. For example, in diabetes management, continuous patterns of pre-meal glucose levels could reveal inadequate basal insulin doses, and exercise-related glucose drops might indicate the need for personalized activity-based insulin adjustments [55].

Such insights support more personalized medical approaches. Cardiac pacemakers can be programmed with patient-specific parameters derived from RWE findings. Insulin pumps can adjust delivery algorithms to reflect individual metabolic patterns. Neurostimulators can modify stimulation intensity according to patient activity levels. Personalization can also include customized rehabilitation programs for orthopedic patients or individualized alert thresholds in remote monitoring devices. All these adaptations are driven by continuous analysis of RWE.

AGENTIC AI APPLICATIONS

Agentic or autonomous AI systems mark a significant progression in RWE utilization. Driven by large language models and specialized medical AI, these agents autonomously analyze data streams and execute complex research tasks. In RWE contexts, agentic AI can systematically query databases from multiple connected devices, synthesize patient histories across different therapeutic areas, and identify safety signals without requiring constant human oversight.

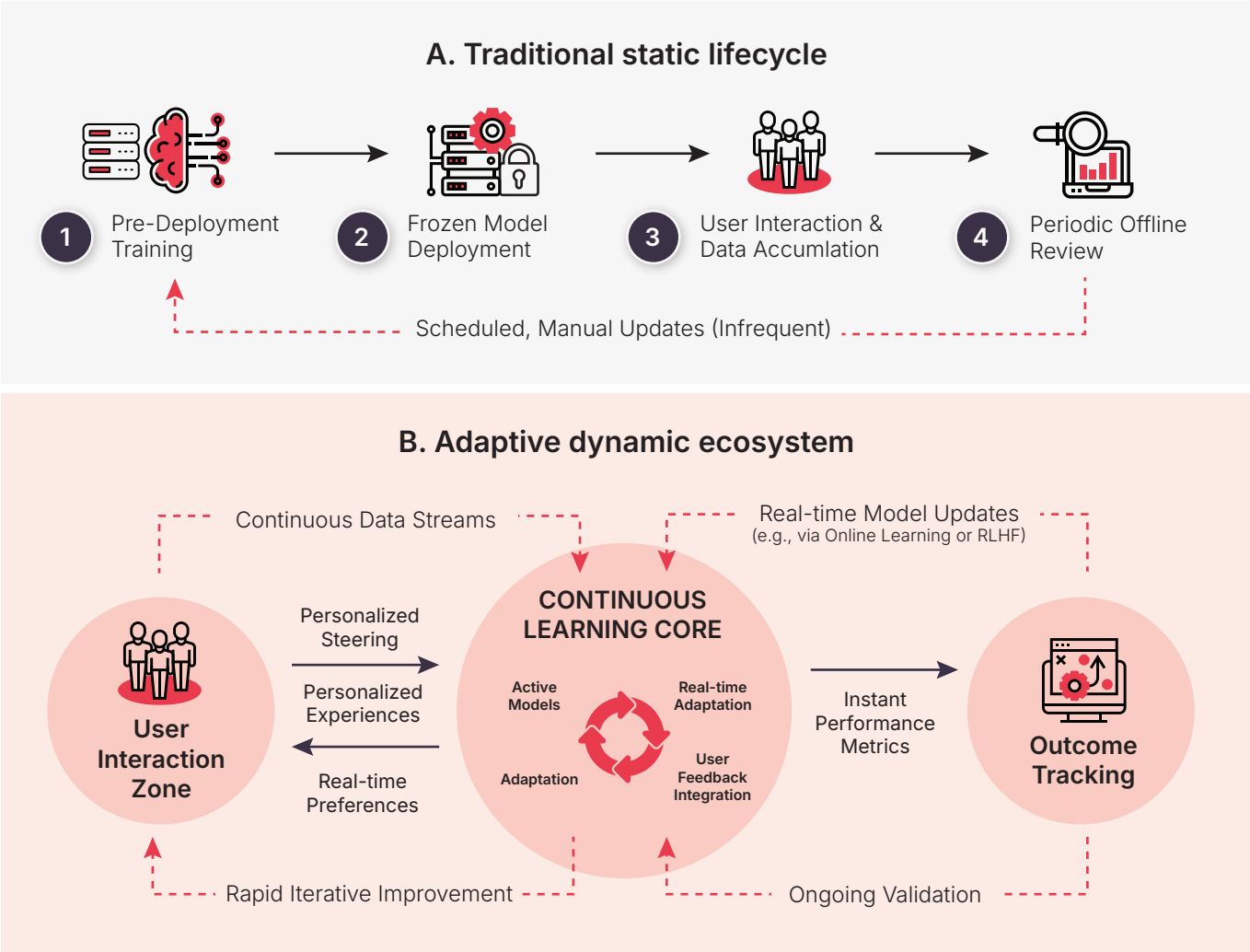
Consider a scenario where an AI agent continuously monitors a registry of AID system users across multiple healthcare systems. Unlike a standard dashboard that simply displays data, this "agent" acts as a digital assistant. It might independently detect an unusual pattern of occlusion alarms in a specific infusion set lot under certain temperature conditions and immediately flag this for engineering review. Furthermore, this technology supports the creation of digital twins, which are virtual models of a patient's unique physiology. By simulating how a specific patient's "twin" reacts to insulin adjustments in a virtual environment, the agent can predict optimal settings before they are applied to the real patient, reducing the risk of hypoglycemia [56]. These agentic AI tools enable advanced data processing, comprehensive analysis, and sophisticated pattern recognition across massive, heterogeneous RWD sets. They can also take on time-intensive research tasks, such as reviewing published literature for emerging safety signals or generating analysis reports that meet regulatory requirements.

SUPPORTING INNOVATION AND DECISION-MAKING

Agentic AI empowers researchers to navigate the complexities of healthcare data more efficiently while supporting precision medicine through personalized treatment recommendations based on comprehensive patient data analysis. However, for AI-based devices that evolve over time, traditional "static" clinical studies are often insufficient. A new paradigm is emerging: Dynamic Deployment, where clinical study is not a one-time event but a continuous process. Rosenthal et al. propose dynamic deployment frameworks in which clinical studies are designed to evolve alongside AI-based medical devices, enabling continuous learning, monitoring, and validation rather than evaluation of a static algorithm [57] (Figure 2).

Validating such adaptive algorithms, which naturally evolve their decision-making logic, requires a regulatory framework that moves beyond the "frozen software" model. This need is increasingly recognized by regulatory pathways such as the Predetermined Change Control Plan (PCCP) [58]. A PCCP allows manufacturers to pre-specify how an AI algorithm will be re-trained and updated based on new RWD without requiring a new regulatory submission for every change. For example, a manufacturer of an AID system could utilize a PCCP to automatically update its meal-detection algorithm based on RWD. Instead of running a new pivotal study for every software tweak, the "local, recurring trial" model allows the device to adapt safely. RWE analysis confirms that the update improves Time in Range without introducing safety risks, validating the change in real-time. This approach aligns with recent expert consensus on AI-driven clinical decision support systems, which emphasizes that AI should continuously assist healthcare professionals and patients to minimize treatment inertia and optimize outcomes [59].

Figure 2. Comparison of static and dynamic models (adapted from Rosenthal et al. [57])



Challenges and Solutions

While fully DCS offers scalability and efficiency, removing the physical site introduces specific operational and regulatory hurdles that must be systematically addressed:

Remote Methodology (Selection Bias and Digital Exclusion)

Challenges: Fully DCS rely heavily on digital recruitment and patient-owned technology. This creates a "digital divide" where participants may be younger, more tech-savvy, and/or have better socioeconomic status than the general patient population. This selection bias can limit the generalizability of findings to the broader, less digitally literate population (e.g., the elderly).

Solution: Use multi-channel recruitment strategies that go beyond social media (e.g., partnerships with community pharmacies or mailers) to reach diverse demographics. Statistical weighting can also be applied during analysis to adjust for underrepresented groups.



Data Quality and Verification in Decentralized Setting

Challenges: In traditional studies, a coordinator verifies data against source documents. In fully decentralized models, much of the data is patient-reported or comes directly from devices without human verification. This creates risks of missing data (e.g., a patient forgets to sync their device) or inaccurate reporting of adverse events (e.g., a patient fails to recognize a symptom as significant).

Solution: Automated data pipelines can flag missing information in real time and trigger automated reminders to the patient. For critical endpoints, implement "eSource" data capture where the digital entry is the source document, supported by audit trails. Using validated digital biomarkers (e.g., sensor-derived metrics) as primary endpoints to reduce the reliance on subjective patient reporting.

Privacy and Data Security in Decentralized Setting

Challenges: Decentralization moves data transmission from secure hospital networks to patients' home Wi-Fi and personal cellular networks. This expands the attack surface for potential cybersecurity threats. Additionally, complying with GDPR is more complex when data flows directly from a patient's home device to a cloud server, potentially crossing borders without a local site as an intermediary controller.

Solution: Organizations must implement end-to-end encryption for all data transmission and robust authentication (e.g., multi-factor authentication) for patient apps. All cloud platforms should be ISO 27001 certified and GDPR-compliant with clear data residency controls. "Privacy-by-design" principles should be used to collect only the minimum necessary data and pseudonymize it at the point of collection.

Regulatory and Payer Acceptance (The EU Gap)

Challenges: While the FDA has demonstrated acceptance of fully DCS to address post-market surveillance requirements (e.g., Loop, CLIO, and Twiist-PS studies), European regulators remain cautious. The primary hurdle in the EU is the independent verification of safety data. Authorities may be concerned that without site visits, serious adverse events may be under-reported or misclassified, and laboratory values (e.g., HbA1c) cannot be verified against a certified lab report.

Solution: To bridge this gap and technically overcome these limitations in Europe, we propose a three-pillar technical framework:

1. Direct EHR Integration: API connections to participants' electronic health records allow for the automated retrieval and verification of diagnoses and lab results directly from routine care providers. This serves as independent source data verification without a study site.

2. Automated Safety Detection via Wearables: Advanced algorithms on smartwatches can automatically detect physiological safety signals, such as arrhythmia, falls, or severe hypoglycemic tremors, independent of patient recall. This provides an objective safety net that operates 24/7.

3. Leveraging National Databases: Specifically for the French market, studies can be designed to link with the National Health Data System. By cross-referencing study data with national claims and hospitalization records, manufacturers can provide the longitudinal, exhaustive safety follow-up required by the HAS. This ensures that major adverse events (e.g., hospitalization) are captured even in a fully remote setting.

Recent European experience further supports the operational feasibility of DCS execution. Nørgaard et al. demonstrated that a fully remote type 2 diabetes study conducted in Denmark could successfully implement social-media recruitment, electronic informed consent, telemedicine visits, remote questionnaires, and connected-device data collection while maintaining high participant adherence and satisfaction [60]. These findings suggest that many logistical and participant-engagement barriers traditionally associated with decentralized studies can now be effectively addressed within European healthcare environments. However, the study primarily evaluated operational feasibility rather than regulatory-grade endpoint validation, leaving unresolved questions regarding independent verification of safety outcomes and clinically adjudicated endpoints outside conventional site infrastructures.

Despite these technological and methodological advances, fully DCS still face structural limitations in achieving equivalence with site-based data verification, particularly for clinically adjudicated endpoints and safety outcomes. While integration with electronic health records, wearable-derived biomarkers, and national databases can partially mitigate these gaps, their availability and interoperability remain inconsistent across healthcare systems. As a result, hybrid models continue to be the most reliable approach for generating evidence acceptable to regulators and payers in many contexts. Fully decentralized designs are viable only when alternative data sources provide comparable levels of validation, traceability, and completeness.



Conclusion

Hybrid DCS currently represents the most operationally and regulatorily viable approach for generating regulatory-grade RWE in Europe. While fully decentralized models demonstrate significant scalability potential, widespread adoption will depend on improved interoperability, validated remote safety verification, and harmonized regulatory expectations across jurisdictions. Manufacturers that invest early in decentralized infrastructure, interoperable data ecosystems, and robust digital quality frameworks will be better positioned to support future reimbursement, post market surveillance requirements, and lifecycle evidence-generation requirements.

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