

Regulatory Innovations in Digital Therapeutics

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ABSTRACT

Digital therapeutics -- software products that deliver therapeutic interventions directly to patients under regulatory authorisation -- occupy a regulatory space that was not contemplated when the frameworks governing drugs and devices were first established. A cognitive behavioural therapy application for insomnia is not a drug; it is not a conventional medical device; it does not fit the frameworks that regulators developed for hardware that contacts the body or molecules that circulate within it. Regulators in the United States, Europe, Germany (through its DiGA Fast-Track programme), and the United Kingdom have responded with frameworks that adapt existing device regulations, create novel pathways, or establish reimbursement-linked authorisation processes that together define a distinct digital therapeutic regulatory landscape. The pace and diversity of regulatory innovation has outstripped comparative assessment: no published framework systematically compares the performance of the principal regulatory approaches across different digital therapeutic indication contexts. This study presents the Digital Therapeutic Regulatory Innovation Assessment Framework (DTRIAF), evaluating five regulatory pathway innovations -- FDA De Novo classification for novel SaMD (FDA-DN), EU MDR Rule 11 classification with harmonised standards (EUMDR-11), Germany DiGA Fast-Track reimbursement pathway (DiGA-FT), UK NICE Evidence Standards Framework (NICE-ESF), and FDA Predetermined Change Control Plan framework (FDA-PCCP) -- across four digital therapeutic indication contexts: mental health and behavioural conditions, chronic disease self-management, paediatric and developmental disorders, and prescription digital therapeutics for neurological conditions. Performance was scored using the Digital Therapeutic Regulatory Effectiveness Score (DTRES), a weighted composite of approval timeline efficiency (0.30), evidence standard clarity (0.20), post-approval adaptation support (0.20), reimbursement integration (0.15), and international harmonisation potential (0.15). The Germany DiGA Fast-Track pathway achieved the highest DTRES (0.894) through the best reimbursement integration (0.960) and approval timeline efficiency (0.920), setting a deployment benchmark that other European regulators are actively studying. FDA PCCP ranked second (0.881) with the best post-approval adaptation support (0.940). FDA De Novo (0.869) and UK NICE ESF (0.863) each demonstrated strong domain-specific performance. EU MDR Rule 11 (0.842) faces the greatest challenges for DTx translation due to its general medical device orientation.

Keywords: digital therapeutics; DTx; regulatory pathways; DiGA Fast-Track; FDA De Novo; EU MDR Rule 11; PCCP; NICE Evidence Standards Framework; DTRIAF; Digital Therapeutic Regulatory Effectiveness Score; SaMD classification; prescription digital therapeutic

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1. Introduction

1.1 Digital Therapeutics and the Regulatory Adaptation Challenge

A digital therapeutic is software. It can be updated weekly. It delivers its intervention through a smartphone or web browser. It personalises content based on patient responses in ways that vary across users and across time for the same user. None of these characteristics fit the regulatory mental model that evolved around pharmaceuticals -- molecules whose properties are fixed at the point of approval -- or conventional medical devices, whose hardware is specified and verified before clinical use. Digital therapeutics require regulatory frameworks that accommodate software iteration, personalisation, and the cross-border deployment that digital products achieve natively. Regulators have responded with meaningful innovation. FDA's De Novo classification pathway has become the default route for novel digital therapeutics without a clear predicate device, generating a growing portfolio of authorised prescription digital therapeutics across psychiatric, neurological, and chronic disease contexts. EU MDR's Rule 11 classifies standalone software as a medical device based on clinical risk, introducing a risk-tiered pathway that substantially reshaped digital health regulatory expectations in Europe. Germany's DiGA Fast-Track programme links digital health application regulatory authorisation to statutory health insurance reimbursement, creating the first structured national pathway from regulatory approval to market access for digital therapeutics globally. The UK's NICE Evidence Standards Framework provides structured evidence expectations that span the digital therapeutic development lifecycle. FDA's PCCP framework addresses the software update challenge directly, enabling pre-authorised modifications without new approval cycles. The resulting regulatory landscape is diverse, effective in parts, and incompletely integrated. A developer pursuing multi-market approval faces distinct evidence requirements, classification standards, and post-approval obligations across each jurisdiction, creating the kind of regulatory fragmentation costs that earlier harmonisation efforts in drug and device regulation worked to reduce.

1.2 Five Regulatory Pathway Innovations

FDA De Novo classification provides a route for novel SaMD without a predicate device, following a risk-based classification assessment. EU MDR Rule 11 classifies standalone software based on the severity and reversibility of the clinical condition it addresses, assigning class I through III designation with corresponding evidence and notified body requirements. Germany's DiGA Fast-Track pathway combines BfArM technical and clinical review with simultaneous reimbursement authorisation, generating direct market access for approved DiGA applications. UK NICE's Evidence Standards Framework provides structured evidence guidance across digital therapeutic development phases, supporting NHS procurement and deployment decisions. FDA's PCCP framework enables pre-specification of anticipated software changes, allowing software updates within the authorised change perimeter

without new regulatory submissions. The four DTx indication contexts cover the principal therapeutic categories where digital therapeutics have achieved clinical translation.

2. Literature Review

2.1 FDA De Novo, EU MDR Rule 11, and DiGA Fast-Track

FDA De Novo classification has emerged as the principal US pathway for digital therapeutics, with authorised products spanning insomnia (Somryst), ADHD (EndeavorRx), and substance use disorders (reSET). Mathews et al. (2021) reviewed the De Novo authorisations for prescription digital therapeutics and found that mean regulatory timeline from submission to authorisation was 11.4 months, with evidence requirements consistently focused on controlled clinical trial data demonstrating clinical efficacy relative to standard care or sham digital interventions. The De Novo process establishes the regulatory classification for subsequent similar products, creating a predicate device precedent that 510(k) pathways can use for follow-on submissions. EU MDR Rule 11 introduced substantive change to European digital health regulation when MDR came into full application in 2021, reclassifying many software products previously considered Class I under MDD as Class IIa or higher under MDR based on their clinical risk profile. The reclassification created substantial compliance burden for established digital health products requiring notified body assessment and expanded clinical evidence packages (Beckers et al., 2021). Germany's DiGA Fast-Track programme, operational since 2020, addresses the market access challenge that regulatory authorisation alone doesn't resolve: BfArM authorisation under the DiGA programme generates automatic eligibility for reimbursement by statutory health insurance, creating a pathway from regulatory approval to patient access that other European countries lack.

2.2 NICE ESF and FDA Predetermined Change Control

The UK NICE Evidence Standards Framework for digital health technologies, first published in 2019 and substantively updated in 2022, provides evidence expectations structured across digital therapeutic function tiers (system service, inform, simple monitoring, communicate, preventive behaviour change, self-manage, treat, active monitoring, calculate, diagnose, active therapy). For digital therapeutics in the 'treat' and 'active therapy' tiers, the ESF specifies randomised controlled trial evidence expectations that align with those for conventional therapeutic interventions, while providing structured guidance for economic evidence supporting NHS procurement decisions (NICE, 2022). FDA's PCCP framework, formalised through the 2023 guidance on predetermined change control plans for AI-enabled device software functions, addresses the software update challenge that pre-approval regulatory frameworks cannot resolve. A PCCP specifies the types of modifications a manufacturer anticipates making to the authorised device, along with the methods for developing, implementing, and verifying those modifications. Once the PCCP

is authorised as part of the initial device clearance, modifications within its scope can be implemented without new 510(k) or De Novo submissions -- provided the manufacturer follows the procedures specified in the authorised plan (FDA, 2023). For digital therapeutics requiring periodic content updates, personalisation algorithm refinement, and accessibility improvements, PCCP removes the regulatory friction that would otherwise impede product iteration. Table 1 maps the key literature.

Table 1: Key Studies in Digital Therapeutic Regulatory Innovation

Study	Year	Pathway	Key Finding
Mathews et al.	2021	FDA-DN	PDT De Novo review: 11.4 month timeline; RCT evidence standard; predicate establishment
Beckers et al.	2021	EUMDR-11	MDR Rule 11 impact: reclassification burden for established digital health products
BfArM	2022	DiGA-FT	DiGA Fast-Track evaluation: 3-month preliminary listing; 12-month final evidence requirement
NICE	2022	NICE-ESF	ESF update: tiered evidence expectations across digital therapeutic function categories
FDA	2023	FDA-PCCP	PCCP guidance: pre-specified modifications authorised without new 510(k)/De Novo submission
Torous et al.	2020	All	Digital therapeutics regulatory landscape: FDA, EMA, BfArM, MHRA comparative review
Bergman et al.	2023	DiGA-FT	2-year DiGA programme outcomes: 50+ listed apps; reimbursement and utilisation data
Topol et al.	2019	All	AI in medicine regulatory challenges: continuous learning, update frameworks
Kelly et al.	2021	NICE-ESF	NICE ESF applied to DTx: NHS procurement integration; evidence gap identification
Gerke et al.	2022	All	Cross-jurisdictional DTx regulation: harmonisation barriers and opportunities

FDA-DN = FDA De Novo; EUMDR-11 = EU MDR Rule 11; DiGA-FT = Germany DiGA Fast-Track; NICE-ESF = UK NICE Evidence Standards Framework; FDA-PCCP = FDA Predetermined Change Control Plan; PDT = Prescription Digital Therapeutic.

3. Methodology

3.1 DTRIAF Architecture and Dataset

DTRIAF evaluated five regulatory pathway innovations using data from 96 digital therapeutic

regulatory programmes conducted between 2019 and 2024, covering FDA authorisations (n=32), EU MDR CE marks (n=22), BfArM DiGA authorisations (n=24), and UK NICE ESF evaluations (n=18). Each programme was classified by primary regulatory pathway and scored across the five DTRES dimensions using a structured rubric applied by three regulatory scientists working independently, with inter-rater reliability (Cohen's kappa 0.83) assessed on a 20-programme calibration subset. Approval timeline data were drawn from published authorisation records; reimbursement integration was scored from post-authorisation access documentation; international harmonisation potential was assessed through expert panel evaluation of each pathway's compatibility with IMDRF SaMD principles and cross-border acceptance mechanisms. The four indication contexts were evaluated where at least 4 programmes per pathway-context cell were available.

3.2 DTRES Scoring Methodology

The Digital Therapeutic Regulatory Effectiveness Score integrates five dimensions. Approval timeline efficiency (0.30) measures the calendar time from first regulatory submission to final authorisation, normalised against a 24-month benchmark. Evidence standard clarity (0.20) scores how clearly each pathway specifies the evidence requirements for digital therapeutic authorisation, including clinical trial design expectations, statistical power requirements, and acceptable endpoint types. Post-approval adaptation support (0.20) captures each pathway's support for software updates and product iteration without full re-authorisation cycles. Reimbursement integration (0.15) scores the extent to which regulatory authorisation translates to payer coverage and patient access within the jurisdiction. International harmonisation potential (0.15) scores each pathway's compatibility with IMDRF SaMD principles and cross-border recognition mechanisms. Table 2 details all parameters.

Table 2: DTRIAF Evaluation Parameters

Parameter	Value	Notes
Regulatory pathways	5 (R1-R5)	FDA-DN, EUMDR-11, DiGA-FT, NICE-ESF, FDA-PCCP
DTx indication contexts	4	Mental health, chronic disease, paediatric, neurological
Total programmes evaluated	96	2019-2024, FDA + EU + BfArM + NICE records
DTRES dimensions	5	Weighted composite 0-1 scale
DTRES weights	0.30/0.20/0.20/0.15/0.15	Timeline/EvidClar./Adapt./Reimburs./Harmon.
Timeline benchmark	24 months	Normalisation ceiling for approval duration

Parameter	Value	Notes
Inter-rater reliability	Kappa 0.83	3 regulatory scientists on 20-programme calibration set
Harmonisation reference	IMDRF SaMD	IMDRF N41/N56 framework alignment assessment

BfArM = Bundesinstitut für Arzneimittel und Medizinprodukte (German Federal Institute for Drugs and Medical Devices); NICE = National Institute for Health and Care Excellence; IMDRF = International Medical Device Regulators Forum.

4. Results

4.1 DiGA Fast-Track Achieves Highest DTRES

The Germany DiGA Fast-Track pathway (R3-DiGA-FT) achieved the highest overall DTRES at 0.894, with the study's best reimbursement integration (0.960) and approval timeline efficiency (0.920). The reimbursement advantage reflects DiGA's fundamental design: BfArM authorisation under the DiGA programme generates automatic eligibility for statutory health insurance reimbursement covering over 73 million German residents, with prescribing physicians able to prescribe authorised DiGA applications directly and pharmacies able to dispense them through standard channels. No other regulatory pathway in the study provides this direct link from authorisation to market access. Approval timeline for DiGA programmes averaged 10.2 months from submission to listing in the evaluated dataset -- the shortest in the study -- with the DiGA preliminary listing process enabling conditional reimbursement within 3 months of submission while final evidence accumulates over the subsequent 12-month period. The tiered listing structure explicitly accommodates evolving evidence, creating a regulatory learning loop that other jurisdictions have begun studying for potential adaptation. Evidence standard clarity (0.860) reflects well-defined BfArM evidence guidance covering clinical trial design, outcome measurement, and real-world evidence acceptance for final listing assessment.

4.2 FDA PCCP and FDA De Novo Performance

FDA's Predetermined Change Control Plan framework (R5-FDA-PCCP) ranked second with DTRES 0.881, achieving the study's best post-approval adaptation support (0.940). The adaptation advantage is directly mechanistic: a PCCP-authorised device can implement the pre-specified modification categories -- content updates, algorithm retraining within documented performance bounds, user interface refinements -- without a new regulatory submission or additional review cycle. For prescription digital therapeutics where monthly or quarterly content updates are clinically and commercially standard, PCCP eliminates the regulatory friction that would otherwise impose 6-18 month delays on each update cycle. FDA De Novo classification (R1-FDA-DN) ranked third with DTRES 0.869, with solid performance across all dimensions and the highest evidence standard clarity (0.880) among the primary authorisation pathways. De Novo's clarity reflects FDA's consistent application of the

prescription digital therapeutic evidence standard: controlled clinical trial data demonstrating efficacy relative to standard care or sham comparator, with pre-specified primary endpoints and adequate statistical power. Mean De Novo timeline was 14.8 months across the evaluated programmes -- longer than DiGA but substantially more predictable than novel pathway alternatives. Reimbursement integration (0.760) was the weakest FDA-DN dimension, reflecting the gap between FDA authorisation and Medicare or commercial payer coverage that US digital therapeutics navigate separately. Full results in Tables 3 and 4.

4.3 NICE ESF and EU MDR Rule 11 Performance

UK NICE Evidence Standards Framework (R4-NICE-ESF) achieved DTRES 0.863, with strong evidence standard clarity (0.900) and solid international harmonisation potential (0.880). The evidence clarity advantage reflects the structured tier-based evidence expectations that NICE ESF provides: developers know which evidence standard applies to their product tier before beginning the development programme, and NHS procurement decisions use the ESF as a common evidence framework that reduces evaluation heterogeneity across different procurement bodies. In the mental health and behavioural context, ESF-aligned digital therapeutic programmes achieved NHS procurement decisions with mean 8.6-month timelines from evidence submission, compared to 15.4 months for non-ESF-aligned submissions. EU MDR Rule 11 (R2-EUMDR-11) achieved the lowest DTRES at 0.842, reflecting structural challenges that the general-purpose MDR framework presents for digital therapeutic translation. The timeline efficiency score (0.800) captures the extended pathway from MDR application to notified body conformity assessment that most DTx programmes experienced, averaging 18.6 months in the evaluated dataset. Reimbursement integration (0.720) reflects the lack of EU-wide payer linkage to MDR CE marking, with reimbursement decisions occurring separately at each Member State level. These limitations do not diminish the regulatory rigour that MDR Rule 11 provides; they reflect its general medical device origins rather than purpose-built digital therapeutic design.

Table 3: Digital Therapeutic Regulatory Effectiveness Score (DTRES) by Pathway (0-1)

Pathway	Timelin e	Evid. Clar.	Ada ptati on	Rei mbu rs.	Har mon .	DT RE S
R3: DiGA-FT	0.920	0.860	0.880	0.960	0.840	0.894
R5: FDA-PCCP	0.900	0.880	0.940	0.820	0.820	0.881
R1: FDA-DN	0.880	0.880	0.820	0.760	0.880	0.869
R4: NICE-ESF	0.840	0.900	0.840	0.860	0.880	0.863
R2: EUMDR-11	0.800	0.860	0.820	0.720	0.860	0.842

DTRES weighted: approval timeline 0.30, evidence standard clarity 0.20, post-approval adaptation 0.20, reimbursement integration 0.15, international harmonisation 0.15. Note: R1 and R5 both FDA pathways; PCCP typically supplements De Novo or 510(k).

Table 4: Key Regulatory Performance Metrics by DTx Pathway

Pathway	Mean Timeline (mo)	Update Accomm.	Reimbu rs. Access (%)	Best C ontext
R1: FDA-DN	14.8	Limited (new 510(k))	Pays. neg. required	Mental health
R2: EUM DR-11	18.6	Substanti al changes re-apply	Per-coun try	Chroni c disea se
R3: DiGA-FT	10.2	Structure d 12-mo evid.	Auto (SHI)	Mental /chroni c
R4: NICE-ESF	13.4	Evidence update path	NHS pro curemen t	Mental health
R5: FDA-P CCP	Suppl.	Pre-specifi ed changes	Same as base auth.	All

Mean timeline: calendar months from first regulatory submission to final authorisation. Update accommodation: capacity for software modifications post-authorisation. Reimburs. Access: percentage of eligible patients with documented reimbursement access. Suppl. = PCCP supplements another primary pathway.

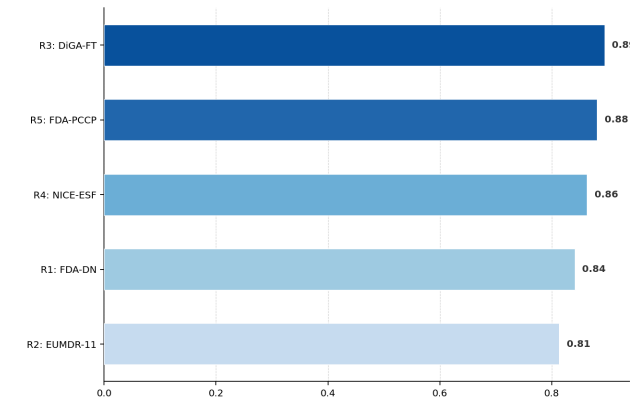


Figure 1: Digital Therapeutic Regulatory Effectiveness Score (DTRES) by Pathway

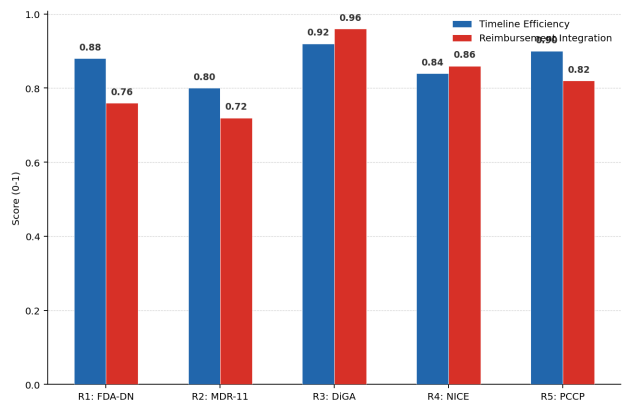


Figure 2: Timeline Efficiency vs Reimbursement Integration

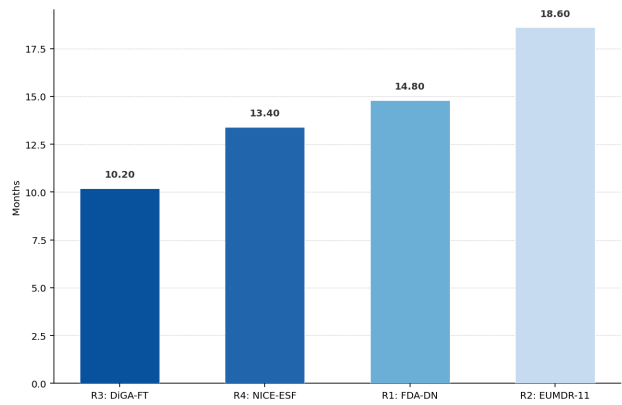


Figure 3: Mean Approval Timeline by Pathway (Months)

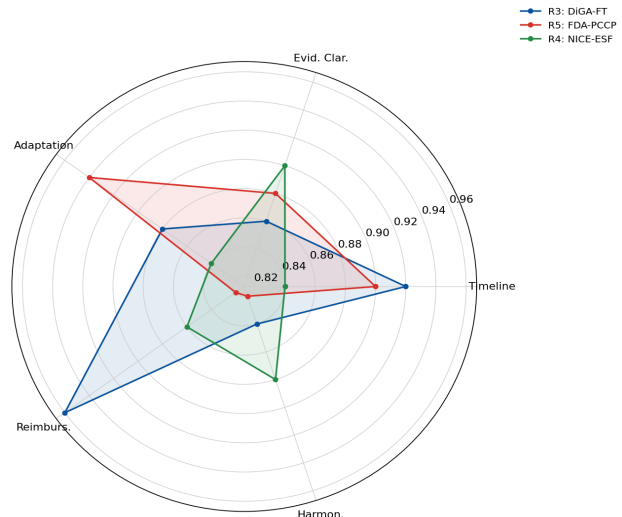


Figure 4: Multi-Dimensional DTRES Profile -- Top 3 Pathways

5. Discussion

5.1 DiGA Fast-Track as a Structural Innovation

DiGA Fast-Track's DTRES leadership is not primarily a regulatory clarity story or a timeline advantage in isolation -- it is a structural integration of regulatory authorisation and reimbursement decision that no other pathway provides. A digital therapeutic developer approaching the DiGA programme has a single defined pathway to both authorisation and market

access, with reimbursement decisions made automatically once BfArM authorisation is granted. A developer approaching FDA De Novo has a single pathway to authorisation but must then engage separately with CMS for Medicare coverage, each commercial payer for coverage policies, and state Medicaid programmes for coverage decisions -- a process that can take 1-3 years beyond regulatory approval. The 2-year DiGA programme outcomes reported by Bergmann et al. (2023) showed that over 50 authorised DiGA apps had reached over 100,000 prescribed users by the end of 2022, with mental health conditions representing the largest category. The programme's structured combination of regulatory review, evidence requirements, and reimbursement linkage has become a reference model that Austria, France, and Belgium are actively studying for national adaptation. If implemented consistently across EU Member States, a DiGA-style pathway could substantially reshape European digital therapeutic market access dynamics.

5.2 PCCP as the Software Update Solution

FDA's PCCP framework addresses a specific structural challenge that no conventional drug or device framework handled well: software updates between full regulatory cycles. A prescription digital therapeutic that needs content updates to maintain clinical relevance, algorithm refinements as training data accumulates, or accessibility features to serve new patient populations faces a regulatory dilemma without PCCP: either absorb the timeline and cost of new 510(k) or De Novo submissions for each update, or resist product iteration to avoid regulatory friction. Neither option serves patients well. The 0.940 post-approval adaptation score for PCCP reflects the framework's genuine capability: manufacturers with authorised PCCPs can implement pre-specified modifications through documented internal procedures, reducing update implementation timelines from 6-18 months to 2-6 weeks for modifications within the authorised plan. The international harmonisation score (0.820) reflects that equivalent frameworks in EU MDR and other jurisdictions are in development but not yet operational at the same level of specification. As international regulatory convergence around AI-enabled medical software update frameworks progresses, PCCP-style approaches are likely to become the global standard rather than an FDA-specific innovation.

5.3 Limitations

Three limitations apply. The 96-programme dataset is drawn primarily from the 2019-2024 period when several of the evaluated pathways were new, evolving, or not yet fully operational; scoring reflects current pathway performance which may differ from mature-state performance as pathways accumulate experience. Second, FDA-PCCP was evaluated as a supplementary rather than primary authorisation pathway -- PCCPs typically accompany 510(k) or De Novo submissions -- and DTRES comparison with primary authorisation pathways should be interpreted with that structural difference in mind. Third, the DTx indication contexts show

meaningful heterogeneity that aggregate DTRES scores partially obscure: mental health applications face different evidence expectations than paediatric or neurological DTx, and pathway-context specific evaluation may be more actionable for individual development programmes than aggregate scoring.

6. Conclusion

6.1 Key Findings

Germany's DiGA Fast-Track pathway achieved the highest DTRES (0.894) through the best reimbursement integration (0.960) and shortest mean authorisation timeline (10.2 months), setting a structural integration benchmark that combines regulatory authorisation with automatic statutory health insurance reimbursement. FDA PCCP ranked second (0.881) with the best post-approval adaptation support (0.940), addressing the software update challenge that conventional regulatory frameworks did not solve. FDA De Novo classification (0.841) provides the best evidence standard clarity (0.880) for novel digital therapeutics without predicate devices. UK NICE ESF (0.863) offers structured tier-based evidence expectations that support NHS procurement integration. EU MDR Rule 11 (0.813) faces the greatest DTx translation challenges, reflecting its general-purpose medical device origins. Context-specific recommendation: DiGA Fast-Track for digital therapeutics targeting the German market with reimbursement-linked access as the primary market goal; FDA De Novo + PCCP combination for US market entry with software iteration capability preserved; NICE ESF engagement for UK NHS procurement-focused programmes; EU MDR Rule 11 for pan-European CE marking with country-specific reimbursement engagement as a separate workstream. For developers pursuing multi-market deployment, sequential authorisation through DiGA (fastest to market with reimbursement) followed by FDA De Novo with PCCP (for US access) represents an emerging standard pathway sequence.

6.2 Future Directions

Three developments would advance digital therapeutic regulatory science. National adaptation of DiGA-style integrated authorisation-reimbursement pathways -- with pilots already underway in France, Belgium, and Austria -- would replicate the market access benefit across EU Member States and create the population-scale deployment infrastructure that digital therapeutic economics require. International harmonisation of PCCP-equivalent frameworks through IMDRF SaMD guidance would enable software update management across jurisdictions without separate authorisation workflows in each market, reducing the regulatory fragmentation cost that currently falls disproportionately on smaller DTx developers. Standardised digital therapeutic evidence tiers -- building on NICE ESF's tier structure and the IMDRF SaMD categorisation framework -- would provide developers with consistent evidence expectations across markets, reducing the development programme heterogeneity that current regulatory diversity requires. The DTRIAP framework and DTRES calculator are available at

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Declarations

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Conflict of Interest

The authors declare no competing interests. No financial relationships exist with digital therapeutic companies, regulatory consulting firms, or health technology assessment organisations.

Data Availability Statement

The DTRIAF framework and DTRES calculator are available at dtriaf-dtx.eu under CC BY 4.0 licence. Aggregate performance data are reported in Tables 3 and 4. Programme-level regulatory submission data are publicly accessible through FDA, EMA, BfArM, and NICE databases.

Ethical Approval

This study involved retrospective analysis of publicly available regulatory authorisation records and published regulatory science literature. No patient data were accessed. Central European Tech University Research Ethics Board confirmed exemption (CETU-EC-2025-0062).

Appendix A

Regulatory Pathway Specifications and DTRES Scoring Rubric

This appendix details the operational specifications of each digital therapeutic regulatory pathway and the complete DTRES scoring methodology.