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STRATIFYHF

STRATIFYHF Artificial intelligence-based decision support system for risk stratification and early detection of heart failure in primary and secondary care	
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Executive summary

The digital transformation of healthcare systems is no longer a futuristic goal—it has become an essential strategy for addressing the evolving health challenges faced by the European Region. As technological advancements in health informatics accelerate, there is a growing recognition of the potential that digital solutions hold in fostering better health outcomes, improving healthcare delivery, and enhancing overall well-being[1]. Digital transformation has opened up multiple new perspectives in the cardiovascular field, with rapidly expanding scientific evidence. Beyond important improvements in terms of patient care, these innovations are also capable of reducing costs for our health care system. In the next few years, digital transformation will continue to revolutionize the field of cardiovascular medicine and broaden our medical and scientific horizons[2].

Clinical Decision Support (CDS) Software (also known as Clinical Decision Support System – CDSS) can help healthcare providers make treatment decisions and interpret patient data. The increasing development of CDS tools with AI-functionality has spurred the Regulators to develop new regulatory frameworks around the oversight of AI-driven software used as medical devices. However, the Governing Bodies' newest guidance(s) on CDS tools leave a lot of questions for clients as they try to make sense of, and comply with, regulations.

This deliverable provides a public description of the characteristics of the Regulatory Roadmap Report of STRATIFYHF, as a part of the potential Ecosystem of Digital Health in Cardiovascular Disease (CVD) and more specifically in Heart Failure.

The global regulatory bodies work in the field of digital health to maintain the safety, efficacy, and privacy of the patients using digital health tools such as telemedicine, mobile health apps, AI diagnosis tools, virtual diagnosis tools, etc.

Thus, certain regulatory bodies set a set of standards and guidelines for the areas where they are in force for digital health product approval and for the efficient and smooth running of digital health systems.

However, various fundamental barriers can obstruct the successful implementation of digital health interventions. Factors such as digital illiteracy, limited access to the Internet and the affordability of technologies create a "digital divide", which exacerbates already existing inequalities in access to digital health technologies and their potential benefits.

Within the specific deliverable PKNM Solutions will try to identify, analyse and communicate the Regulatory challenges that innovations like the Clinical Decision Support Systems (CDSS) and the Mobile app are facing during the progress of STRATIFYHF. The vast scope of adaptive AI applications in Digital Health Solutions in CVD and, more specifically, in Heart Failure brings along key regulatory challenges. Some of these relate to standards, data access, ethics, real-time data requirements, and demonstrate effectiveness and governance.

This Deliverable Report will show that the regulatory challenges, however, are expected to be significant and require agile and more effective ways of working for regulators, policymakers, health care professionals, patients and health service researchers to be responsive at pace.

[1] *Digital transformation for better health and well-being in the European Region. D. Novillo-Ortiz et al. D. Novillo-Ortiz et al. , International Journal of Medical Informatics 200 (2025) 105908*

[2] *Stremmel C, Breitschwerdt R. Digital Transformation in the Diagnostics and Therapy of Cardiovascular Diseases: Comprehensive Literature Review. JMIR Cardio. 2023 Aug 30;7:e44983. doi: 10.2196/44983. PMID: 37647103; PMCID: PMC10500361.*

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Preamble

"Patients who need and receive timely advanced heart failure (HF) therapies have better long-term survival.

However, many of these patients are not identified and referred as soon as they should be."

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List of Abbreviations

Abbreviation	Explanation
AI	Artificial Intelligence
BIOIRC	Bioengineering Research and Development Centre
CDS	Clinical Decision Support
CDSS	Clinical Decision Support Systems
CHF	Chronic Heart Failure
CVD	Cardiovascular Disease
CVRM	Cardiovascular Risk Management
DHI	Digital Health Inventions
DHT	Digital Health Technologies
DICOM	Digital Imaging and Communications in Medicine
DL	Deep Learning
ECG	Electrocardiogram
EHR	Electronic Health Records
EU	European Union
EUDAMED	European Database on Medical Devices

FDA	Food and Drug Administration
FTC	Federal Trade Commission
GDMT	Guideline-Directed Medical Therapy
GP	General Practitioner
HAZOP	Hazard and Operability Analysis
HF	Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
IMDRF	International Medical Device Regulators Form
ISO	International Organization for Standardization
IVDR	In Vitro Diagnostic Medical Device Regulation
MDR	Medical Device Regulation
mHealth	Mobile Health
MRI	Magnetic Resonance Imaging
NCD	Non-Communicable Diseases
NHS	National Health Services
NLP	Natural Language Processing
NYHA	New York Health Association
PMA	Pre-Market Approval
PMN	Pre-Market Notification
PPG	Photoplethysmography
PREM	Patient-Reported Experience Measures
PROM	Patient-Reported Outcome Measures
RCT	Randomised Controlled Trials
SaMD	Software as a Medical Device
UHC	Universal Health Coverage
WHF	World Heart Federation

1. STRATIFYHF within Digital Healthcare Ecosystem

Rationale: STRATIFYHF aims to be the facilitator of the joint development of innovative instruments, processes and solutions for continuous monitoring, able to provide a means of early warning and detection for prodromal symptomatology and risk stratification in Heart Failure.

The global regulatory bodies work in the field of digital health to maintain the safety, efficacy, and privacy of patients using digital health tools such as telemedicine, mobile health apps, AI diagnosis tools, virtual diagnosis tools, etc.

Thus, certain regulatory bodies establish standards and guidelines for the areas where they are in force for digital health product approval and the efficient and smooth running of digital health systems.

In this context, the aim of the STRATIFYHF is to facilitate policy and regulatory questions in discussions on applicable solutions towards innovation and industrial performance – and the interplay between them, such as the potential outcomes of STRATIFYHF.

Instead of structuring the regulatory report according to traditional input and output indicators, the intention of the Deliverable is to include data that provides rich representations of the vitality of both the **STRATIFYHF's Translational Potential under a compliance canvas according to** its **Regulatory applied Landscape** in an international context.

1.1 STRATIFYHF Revolutionising Digital Healthcare

In this scene, Research Infrastructures such as STRATIFYHF Consortium clearly acts as the bridge between research and industry. STRATIFYHF, as Research Infrastructure, aims to contribute to building the AI-based DSS and a Medical Mobike App enhancing Innovation within the European Union modern research priorities' strategy.

STRATIFYHF Consortium recognizes that rigorous and transparent regulatory mechanisms and guidance on data security and privacy are essential conduits to enhance trust by patients and healthcare providers, ensure ethical use, and support the safe and effective integration of Digital Health Tools into health systems, ultimately contributing to their scalability, sustainability, and impact on population health outcomes.

Over the past two decades, healthcare services have been revolutionized by integrating information technology tools into medical settings worldwide, with the aim of improving the quality of care and saving resources. These tools enabled health systems to adopt Electronic Health Records (EHRs), telemedicine platforms, health monitoring devices, and AI-driven diagnostic tools[3]. Digital health tools can reduce medical errors, enhance day-to-day medical processes, and increase revenue by simplifying billing processes and attracting new patients with convenient access to care[4]. In addition, these tools have proven their immense value during times of global pandemics as they have helped to improve access to care, identify cases early on, and manage the supply chain[5]. Health systems globally, however, encounter enormous technical and legal challenges that hinder the consistent implementation and delivery of these services. These barriers need to be effectively addressed to unlock the full potential of digital health in transforming healthcare in

[3] Patel S, Kongnakorn T, Nikolaou A, et al. Cost-effectiveness of targeted screening for non-valvular atrial fibrillation in the United Kingdom in older patients using digital approaches. J Med Econ. [Internet]. 2023; 26(1):326–334. doi: 10.1080/13696998.2023.217921010.1080/13696998.2023.2179210.

[4] Haleem A, Javaid M, Pratap Singh R, et al. Medical 4.0 technologies for healthcare: features, capabilities, and applications. Internet Things Cyber-Physical Syst. [Internet]. 2022;2:12–30. doi: 10.1016/j.iotcps.2022.04.001.

[5] Lee P, Abernethy A, Shaywitz D, et al. Digital health COVID-19 impact assessment: lessons learned and compelling needs. NAM Perspect. 2022;2022. doi: 10.31478/202201c.

these regions, but starting from an early stage within the research infrastructures. Therefore, these research infrastructures should aim to identify at an early stage specific technical and regulatory challenges of digital health implementation in healthcare settings.

Digital health is revolutionizing the way healthcare is researched, developed, delivered, and experienced. As technological advancements continue to accelerate, they present both opportunities and challenges for healthcare systems worldwide. Policymakers and regulatory bodies are tasked with the critical responsibility of crafting frameworks that ensure the ethical, legal, safe, and secure integration of digital solutions into healthcare. Despite the rapid integration of digital technologies, the development of comprehensive policy frameworks and regulatory mechanisms has lagged, creating a gap that needs urgent attention. Recent studies[6] have highlighted the significance of digital health innovations to improve patient outcomes, enhance healthcare delivery, and reduce costs. Nonetheless, these scientific achievements also raise significant questions about clinical safety, data privacy, and ethical considerations. Addressing these issues requires a concerted effort to develop robust regulatory frameworks that can keep pace with technological innovation while ensuring patient safety and data security.

Digital health technologies can help address these challenges. They may be a tool to reach Sustainable Development Goal 3.4 and reduce premature mortality from non-communicable diseases (NCDs) by a third by 2030. Yet, a range of fundamental barriers prevents implementation and access to such technologies. Health system governance, health provider, patients and technological factors can prevent or distort their implementation.

The integration of digital technology into healthcare systems holds promise for improving services in developing countries, especially in remote and underserved regions. However, various challenges can impede the implementation and sustainability of digital health initiatives. Technical issues in remote areas, political instability leading to policy-related challenges, and inadequate government support hinder progress. Regulatory barriers can create challenges for the effective implementation of digital health interventions. Inconsistent regulations, outdated guidelines, and legal ambiguities can stifle innovation and escalate costs. Weak or absent regulations on insurance coverage for telemedicine and digital health services further limit financial accessibility. To overcome these challenges, recommendations include the introduction of regulatory sandboxes, pre-certification schemes, and increased international collaboration. These approaches aim to strike a balance between robust regulation and fostering innovation in digital health. The accelerated growth of digital health interventions, exacerbated by the COVID-19 pandemic, underscores the urgent need for proactive and continuous regulatory frameworks. These frameworks play a critical role in ensuring safety, maintaining quality, and promoting equitable access. While some countries have temporarily eased regulations in response to the pandemic, achieving a balanced regulatory approach is essential to address new challenges, potential risks, and disparities in healthcare delivery arising from the evolving digital landscape.

[6] *https://www.frontiersin.org/research-topics/63542/navigating-digital-health-balancing-innovation-safety-and-regulatory-challenges/auth*ors

2. Introducing STRATIFYHF to CVD Cluster – Heart Failure

More than 500 million people worldwide live with cardiovascular disease (CVD). Health systems today face fundamental challenges in delivering optimal care due to ageing populations, healthcare workforce constraints, financing, availability and affordability of CVD medicine, and service delivery[7].

World Heart Federation (WHF) efforts aim to identify essential roadblocks on the pathway to effective prevention, detection, and treatment of CVD. Further, they aim to provide actionable solutions and implementation frameworks for local adaptation. This WHF Roadmap for digital health in cardiology identifies barriers to implementing digital health technologies for CVD and provides recommendations for overcoming them[8].

Digitalization in cardiovascular medicine will certainly continue to gain importance in the near future, and it will be crucial to make the best possible use of these technologies. Today, the field of digital cardiovascular medicine has a strong focus on telemedicine technologies, as a lack of interoperability and standardization still limits applications such as automation and intelligent decision support systems, as well as modern medical IT-based research tools. Continual efforts will not only improve patient care but also have significant health economic saving potential for various CVD patterns. It is therefore important not to cling obsessively to old systems but to embrace innovations and actively help to shape them.

Healthcare is highly regulated and serves as one of the largest industrial sectors of the global economy. It accounts for approximately $10 trillion dollars spent annually and includes a complex interrelated web of businesses, vendors, insurers, providers, organizations, and most importantly, patients. Healthcare regulations originate from decades-old frameworks, often ill-suited for the rapid advancement of technological innovation and growth.

Worldwide, the mitigation and adaptation policies linked to Diagnostics' change require a dedicated innovative monitoring capacity. So, a potential large market exists for improved, cost-effective and innovative instrumentation for Cardiovascular Diseases, Heart Failure, and CDSS based on AI Innovation.

In many Research and Healthcare Systems, digital health regulations tend to be disorganized, with multiple bodies exerting control without clearly delineated responsibilities. Fragmented regulations can impede the effective use of digital health technologies, leading to potential health risks and market inefficiencies. Technological developments often outpace the regulatory bodies' abilities to keep up with them, leading to outdated guidelines and legal grey areas that further complicate regulation processes.

Additionally, the absence of regulatory mechanisms to ensure that insurance companies cover telemedicine and digital health services makes these potentially beneficial services financially inaccessible to many individuals, despite their promise for improving access to care.

Example: Clinical decision support may improve cardiac care at low-income community health centres (**Fig. 1**)[9]

[7] *Burden G, Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020; 76: 2982–3021.*

[8] *Tromp J, Jindal D, Redfern J, Bhatt A, Séverin T, Banerjee A, Ge J, Itchhaporia D, Jaarsma T, Lanas F, Lopez-Jimenez F, Mohamed A, Perel P, Perez GE, Pinto F, Vedanthan R, Verstrael A, Yeo KK, Zulfiya K, Prabhakaran D, Lam CSP, Cowie MR. World Heart Federation Roadmap for Digital Health in Cardiology. Global Heart. 2022; 17(1): 59. DOI: https://doi.org/10.5334/ gh.1141*

[9] Dave Fornell | *February 08, 2022 | Cardiovascular Business* | CVIS

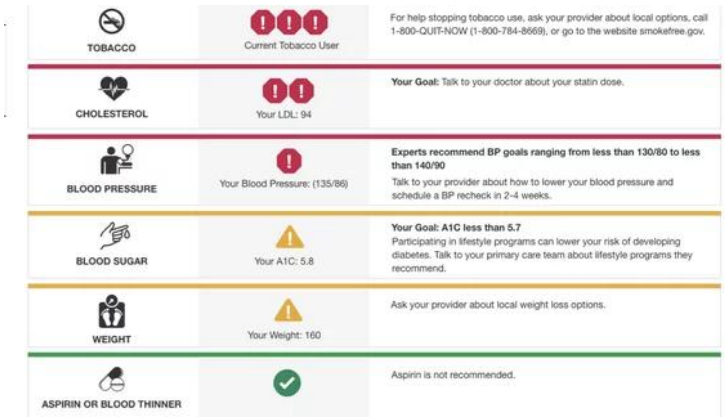

Figure 1. An example of the CV Wizard clinical decision support (CDS) software showing a screen designed to help patients better understand their risks and areas they need to work on.

The authors wrote that evidence-based management of modifiable risk factors for cardiovascular disease can substantially reduce CVD-related morbidity and mortality risks. However, a deficit persists between recommended and observed CVD risk management, especially among vulnerable lower-income patients. One reason for this is that primary care clinicians must consider multiple factors affecting CVD risk for a given patient and determine which to address to optimally affect that patient's risk within a brief encounter. Electronic health record–based CDSS address these barriers by alerting clinicians when patients have uncontrolled CVD risks and suggesting treatment options.

The technology used was the CV Wizard, a non-proprietary, web-based CDSS developed at HealthPartners Institute, a large, nonprofit, integrated healthcare system. The algorithms of the software reflect current CVD care guidelines and account for a patient's blood pressure, laboratory results, distance from goals, medications, and comorbidities.

Digital health technologies, such as electronic decision support tools, telemonitoring, remote monitoring, or mobile health (mHealth) apps, have the potential to help address health system challenges which limit the achievement of optimal and universal health coverage (UHC). These technologies can contribute to UHC by empowering patients[10] and providers[11], promoting universal health services coverage[12], improving long-term patient outcomes and care experience, and reducing healthcare costs[13]. Therefore, Digital Health Interventions (DHIs) may be a tool to reach Sustainable Development Goal 3.4 and reduce premature mortality from NCDs by a third by 2030[14].

[10] *Battineni G, Sagaro GG, Chintalapudi N, Amenta F. The benefits of telemedicine in personalized prevention of cardiovascular diseases (CVD): A systematic review. J Pers Med. 2021; 11. DOI: https:// doi.org/10.3390/jpm11070658*

[11] *Srinivasapura Venkateshmurthy N, Ajay VS, Mohan S, Jindal D, Anand S, Kondal D, et al. m-Power Heart Project – a nurse care coordinator led, mHealth enabled intervention to improve the management of hypertension in India: study protocol for a cluster randomized trial. Trials. 2018; 19(1): 1–9. DOI: https://doi.org/10.1186/s13063-018-2813-2*

[12] *Wilson D, Sheikh A, Görgens M, Ward K. Technology and Universal Health Coverage: Examining the role of digital health. J Glob Health. 2021; 11: 16006. DOI: https://doi.org/10.7189/jogh.11.16006*

[13] *Li R, Liang N, Bu F, Hesketh T. The effectiveness of self-management of hypertension in adults using mobile health: Systematic review and meta-analysis. JMIR mHealth uHealth. 2020; 8: e17776. DOI: https://doi.org/10.2196/17776*

[14] *Countdown N. NCD Countdown 2030: efficient pathways and strategic investments to accelerate progress towards the Sustainable Development Goal target 3.4 in low-income and middle-income countries. Lancet. 2022; 399: 1266–1278. DOI: https://doi.org/10.1016/S0140-6736(21)02347-3*

2.1 Introducing STRATIFYHF Digital Health Tools in CVD – Heart Failure: Regulatory Considerations

Digital Health Technologies (DHT) such as the ones to be developed by STRATIFYHF can help "all of us" address the challenges that health systems face today. They can empower patients and health providers, promote universal health services coverage, improve long-term patient outcomes, and reduce healthcare costs.

Digital health tools could bridge the gaps in heart failure management and improve patient outcomes. Digital health interventions, broadly referring to the use of digital information and technology to advance health, encompass a wide array of tools that include text message programmes, mobile health (mHealth) apps, telehealth consultations, wearable devices, and electronic decision-support tools. Digital tools for managing heart failure should now be prioritised, given the recent COVID-19-driven acceleration of digital tools in medicine and rapid advances in internet connectivity worldwide, including in LMICs[15].

However, a range of fundamental barriers can obstruct the successful implementation of digital health interventions. Factors such as digital illiteracy, limited access to the Internet and the affordability of technologies create a "digital divide", which exacerbates already existing inequalities in access to digital health technologies and their potential benefits.

Decision Support Systems - DSS, *as so called in US "Computerised Clinical Decision Support Systems (CDSSs)",* like the STRATIFYHF DSS will become well-known tools for enhancing evidence-based decisions in clinical practice. According to several studies, DSSs have the potential to influence clinicians' decision-making and to facilitate the implementation of new disease management strategies in everyday clinical work, as they integrate individual patient data with evidence-based recommendations[16].

Heart failure (HF) is a high-morbidity, high-cost condition that is expected to increase in prevalence. Although hospital admissions and readmissions are common in HF, research consistently shows that Guideline-Directed Medical Therapy (GDMT) reduces mortality, hospitalizations, and symptom burden. Because of outdated practice patterns, delays in educational updates, and unclear sharing of medical management responsibilities, health care providers have struggled to successfully implement GDMT. Care for patients with HF should be improved by empowering primary care teams and hospitalists to implement GDMT rather than deferring to cardiology specialists[17].

Incidence of Heart Failure (HF) increased dramatically with age and was greater in men, particularly in the younger strata of the population. Mortality in incident HF patients grew steadily across the age groups; it was tenfold higher in the oldest group and was also higher in men. Globally, an increment in Primary Health Care (PHC) resource utilization is observed after the first episode of HF registered in the clinical records. Several factors have been identified in the literature explaining differences in incidence rates. They include methodologies, diagnosis criteria, and HF approaches employed by local health systems. Moreover, it has been reported that diagnosis could be confirmed in only half of the patients labelled as HF in the PHC records.

Chronic Heart Failure (CHF) is a common condition, especially among the elderly, and is associated with high mortality and morbidity. The burden on the health care system resulting from the management of CHF is rising in parallel with the increasing proportion of elderly persons in the population. In Sweden, CHF is mostly

[15] *Digital tools in heart failure: addressing unmet needs Myhre, Peder L et al. The Lancet Digital Health, Volume 6, Issue 10, e755 - e766*

[16] *BalasEA,AustinSM,MitchellJAetal.Theclinicalvalue of computerized information services: a review of 98 randomized clinical trials. Archives of Family Medicine 1996;5:271–8.*

[17] *A Clinical Decision Support Tool to Advance Guideline-Directed Medical Therapy in Patients with Heart Failure NEJM Catalyst Innovations in Care Delivery, Volume 4 • Number 12 • November 15, 2023*

managed at Primary Healthcare (PHC) Centres. Its management is often complex, and both overdiagnosis and underdiagnosis are common[18]. The guidelines for the treatment of CHF have been revised in the past few years, but GPs' adherence to the guidelines is insufficient[19]. CHF is therefore an important field for studies about the influence of a guideline-based CDSS on GPs' clinical performance.

DSS are often incorporated within EHR systems and integrated with other computer-based functions that offer patient-care summary reports, feedback on quality indicators, and benchmarking. Knowledge management systems that provide access to scientific literature and strategies for CVD prevention may also be linked with CDSS[20].

Clinical decision support systems (CDSS) and Medical Mobile Apps leverage health information technology to provide health care professionals with intelligent decision-making tools, aiming to improve medical quality, reduce errors, and improve patient outcomes[21].

Furthermore, the diverse nature of digital health tools, including mobile health (mHealth) apps, wearables, telemedicine platforms, and EHRs, further exacerbates this complexity in regulatory terms. Another difficult regulatory task is determining whether these tools fall under medical devices, pharmaceuticals, or another category. This complexity stems from the fact that many of these tools overlap multiple categories and that the categories are evolving with technology. As a result, this lack of clarity leads to uncertainty regarding regulatory processes and requirements for each tool. MHealth applications, for instance, fall into a grey area in the existing regulatory framework. Hence, some can be treated as medical devices while others fall outside of stringent regulation requirements, creating potential gaps that leave patients at risk and data security vulnerable[22].

In Conclusion:

STRATIFYHF DSS and STRATIFYHF Medical Mobile App have a great potential for cardiovascular disease prevention (CVD) by enhancing Risk Stratification in Herat Failure, by including::

- Reminders for overdue CVD preventive services (e.g., screening for risk factors such as high blood pressure, diabetes, and high cholesterol),
- Assessments of patients' risk for developing CVD based on their medical history, symptoms, and clinical test results,
- Recommendations for evidence-based treatments to prevent CVD, including intensification of treatment,
- Recommendations for health behaviour changes to discuss with patients (e.g., quitting smoking, increasing physical activity, reducing excessive salt intake),
- Alerts when cardiovascular disease (CVD) risk factor indicators are outside target ranges.

[18] *NilssonGandStrenderLE.Managementofheartfailure in primary health care. A retrospective study on elec- tronic patient records in a registered population. Scandinavian Journal of Primary Health Care 2002;20: 161–5.*

[19] *Halling A and Berglund J. Diagnosis and treatment of heart failure in primary health care among elderly patients with non-insulin-dependent diabetes mellitus, with special reference to use of echocardiography. Scandinavian Journal of Primary Health Care 2003;21: 96–8.*

[20] *Guide to Community Preventive Services. (2013). Heart disease and stroke prevention: clinical decision-support systems (CDSS). Retrieved from https://www.thecommunityguide.org/findings/cardiovascular-disease-clinical-decision-support-systems-cdss*

[21] *A Belard, T Buchman, J Forsberg Precision diagnosis: a view of the clinical decision support systems (CDSS) landscape through the lens of critical care J Clin Monit Comput, 31 (2) (2017), pp. 261-271*

[22] *Maaß L, Freye M, Pan CC, et al. The definitions of health apps and medical apps from the perspective of public health and law: qualitative analysis of an interdisciplinary literature overview. JMIR Mhealth Uhealth. 2022; Oct10(10):e37980. doi: 10.2196/37980.*

3. Purpose

The main purpose of this deliverable is to highlight the technological advancements offered by STRATIFY HF and to relate these innovations to challenges raised by regulatory systems and the scientific community.

Creating a culture for STRATIFYHF digital health technologies by the relevant insights "**Quick takes"** from PKNM Solutions**:**

- As the science behind clinical decision-support tools a- DSS and other digital health solutions such as Medical Mobile Apps advance rapidly, social and cultural changes among healthcare stakeholders are critical to ensure successful adoption,
- By alleviating administrative tasks and manual data entry, artificial intelligence has the potential to foster a closer connection between healthcare professionals and patients,
- Clinical-decision support tools can provide personalized dynamic risk assessments while accommodating patients' individual preferences.

While the integration of digital health technologies and artificial intelligence (AI) in cardiovascular and emergency medicine can transform patient care, these tools can face social and cultural challenges within healthcare institutions that prevent their full implementation[23]. A lack of exposure and/or comfort with AI technologies, concerns around workflow disruption, and a perception that AI is a threat to a clinician's autonomy or professional judgement may impede the adoption of these tools and increase reluctance[24].

Another significant challenge in digital health regulation is the shortage of technical expertise among regulatory staff. This shortfall hinders the successful implementation and oversight of digital health technologies. Those responsible may lack an in-depth understanding of the technologies they regulate, making it difficult to fully grasp potential risks and benefits. This often leads to ineffective, misplaced, or overly restrictive regulations that stifle innovation and diminish the potential health benefits of healthcare provision.

3.1 Intended Audience

The overall purpose of this deliverable is to facilitate reflection among STRATIFYHF partners, relevant Managing Authorities, internal and external actors, and general readers regarding:

- who are the Regulatory actors, who might enhance or influence RA developmental support and reporting towards the Competent Authorities,
- what QA & RA functions they perform in the different phases of innovation processes,
- what skills and competencies they need to develop and possibly acquire in order to support interactive innovation processes.

The description represents a state of the art since it will be entirely based on current literature and experience.

This deliverable is intended to serve as a basic guideline for the Generic Regulatory Analysis and Implementation approach of the STRATIFYHF project. The main goal is for all beneficiaries and not only to understand the Regulatory ecosystem dealing with DSS and Mobile App in CVD. It may also be an informative report for those external parties interested in different aspects concerning STRATIFYHF's innovation potential

[23] *Meskó, B et. Al. (2017). Digital health is a cultural transformation of traditional healthcare. mHealth, 3, 38.*
[24] *Elhaddad, M., & Hamam, S. (2024). AI-driven clinical decision support systems: an ongoing pursuit of potential. Cureus, 16(4).*

and its development, along with the regulatory implications surrounding such a multitasking interdisciplinary effort.

PKNM Solutions emphasizes the transformative potential of clinical decision-support tools – DSS and Medical Mobile Apps in cardiology, in primary care and in emergency medicine. These digital health technologies are already assisting clinicians daily in diagnosing and managing conditions more effectively[25]. However, we highlight a critical gap:

While the science behind these tools is robust and progressing at a rapid pace, their implementation often lags due to social and cultural barriers within healthcare institutions and the friction that adopting new tools in the medical community triggers[26]. *"Science is easy, but people are hard", (Professor Gibson notes).*

The challenge lies in aligning the goals of various stakeholders within hospitals and care settings, rather than achieving the next technological breakthrough. Social and cultural change is crucial to creating a space for innovation within healthcare institutions that can be trusted.

The fast-paced nature of medical science and practice challenges physicians to keep practising concurrent with guidelines and the latest evidence. Some state that health care decision making has never been more complex because of multi-morbidity and different severities of disease clustered in one individual[27].

Last but not least, the audience has to understand the regulatory redefinition of the role of digital health technologies: From manual data entry to guided decision-making.

3.2 STRATIFYHF DSS & Mobike App in Use and potential benefit by Primary Healthcare

Heart failure (HF) is a highly prevalent disease, affecting the elderly in particular[28]. Early diagnosis of HF is important so that treatment can be initiated on time in order to delay progression to overt HF.1 In Europe, most patients with HF first present in primary care[29]. However, HF diagnosis and treatment are often inadequate in primary care.

A 'seamless' system of care, integrating both community and hospital care, has been shown to reduce HF hospitalisation and mortality in patients discharged from hospital[30]. Despite the evidence, multidisciplinary management programmes are still not widely implemented as usual care.

The reasons behind this evidence-practice mismatch have been addressed in qualitative studies exploring the barriers and facilitating factors primary care professionals experience in the management of chronic heart failure (CHF). Special interest is focused on the perceptions of the GP, who plays a key role in the coordination of care for patients with long-term conditions in primary care[31]. Much qualitative research has

[25] *Grant, J.K. et al. Digital health innovation and artificial intelligence in cardiovascular care: a case-based review. npj Cardiovasc Health 1, 26 (2024).*
[26] *Elhaddad, M., & Hamam, S. (2024). AI-driven clinical decision support systems: an ongoing pursuit of potential. Cureus, 16(4).*
[27] *Maddox TM, Albert NM, Borden WB, Curtis LH, Ferguson TB Jr, Kao DP, et al. The learning healthcare system and cardiovascular care: a scientific statement from the American Heart Association. Circulation. 2017;135(14):e826–e57.*
[28] *Ponikowski P mVoors AA, Anker SD,* et al., *Authors/Task Force Members; Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891–975. doi:10.1002/ejhf.592*
[29] *Cleland JG, Cohen-Solal A, Aguilar JC, et al. Management of heart failure in primary care (the IMPROVEMENT of Heart Failure Programme): an international survey. Lancet 2002;360:1631–9. doi:10.1016/S0140-6736(02)11601-1*
[30] *McAlister FA, Stewart S, Ferrua S, et al. Multidisciplinary strategies for the management of heart failure patients at high risk for admission: a systematic review of randomized trials. J Am Coll Cardiol 2004;44:810–19. doi:10.1016/j.jacc.2004.05.055*
[31] *World Health Organization. Primary health care: now more than ever. World Health Report. 2008.*

been undertaken to respond to this issue, but, to date, no review article has synthesised all the previous research. Therefore, this deliverable will also try to address existing communication gaps, while it will synthesize the GPs' needs, perspectives and expectations on current management of CHF in primary care.

GPs' uncertainty in all areas of HF management starts with diagnostic uncertainty. Lack of access to specialised care and lack of knowledge have been identified as important contributors to this uncertainty. Lack of access to specialised care could partly be countered by promoting implementation of natriuretic peptides in primary care, for instance, as a rule-out test to reduce the number of patients needing echocardiography.

Additionally, strategies bringing evidence into practice should be promoted, such as locally drafted guidelines or DSS integrated in the electronic health record, as per STRATIFYHF main aims and core Scope. GPs are constantly expressing the need for a multidisciplinary chronic care approach for HF. However, mixed experiences have been noted with interprofessional collaboration. When establishing new initiatives for HF improvement programmes, the barriers and facilitators found in this evidence synthesis should be taken into account. This is something that this Deliverable is trying to address in the public audience.

One recurring frustration among clinicians is the excessive administrative burden imposed by EHRs and other digital tools they might need to interact with every day[32].

Cardiovascular risk management (CVRM) in high-risk patients requires a comprehensive approach and a lifelong effort of patients that affects lifestyle and dictates adherence to medical treatment of risk factors. CVRM is complex because it involves many risk factors that may change over time. CVRM guidelines provide support and advocate the use of risk prediction algorithms for the identification of patients at risk for (recurrent) cardiovascular events[33].

Treatment decisions, such as starting or intensifying lipid blood pressure lowering treatment, are based on estimated absolute cardiovascular risk in individual patients and their absolute levels of risk factors. Yet, there seems to be a gap between guideline recommendations and daily clinical practice[34].

Adherence to guidelines varies between medical disciplines and between treating physicians, even for similar patients. Completeness of risk factor assessment, pharmacological and non-pharmacological treatment initiation and long-term uptake of treatment in patients with a cardiovascular condition can be further optimized, which potentially leads to a reduction in preventable cardiovascular morbidity and mortality[35].

“MD doesn’t stand for manual data entry.” STRATIFYHF advocates for a shift in which technology supports clinicians, not the other way round. For example, tools that automate data collection, risk assessment, and even scheduling can significantly reduce workload.

http://www.who.int/whr/2008/en/ (30 Mar 2016).

[32] Wosny, M., et. al. (2023). Experience of Health Care Professionals Using Digital Tools in the Hospital: Qualitative Systematic Review. JMIR human factors, 10, e50357.

[33] Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. European guidelines on cardiovascular disease prevention in clinical practice: the sixth joint task force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016;37(29):2315–81.

[34] Jan S, Usherwood T, Brien JA, Peiris D, Rose J, Hayman N, et al. What determines adherence to treatment in cardiovascular disease prevention? Protocol for a mixed methods preference study. BMJ open. 2011;1(2):e000372.

[35] Kotseva K, Wood D, De Bacquer D, De Backer G, Ryden L, Jennings C, et al. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. Eur J Prev Cardiol. 2016;23(6):636–48.

3.3 Overall Objective (s) and Intended Impact: AI Initial Considerations

To date, we have been unable to find any systematic reviews assessing the use of DSS for patients with breathlessness and in Risk Stratification in Heart Failure in primary care and outpatient services, for example, where they may provide the most impact. Hence, systematic research approaches with a clear translational impact, such as that of STRATIFYHF aims to investigate the evidence for DSS in assessing and managing Risk Prediction and Risk Stratification in Heart Failure and its applicability to primary care, are still so seldom and underfunded. We also sought to identify features that are associated with beneficial outcomes as well as unintended consequences in real-world practice.

The contribution of STRTIFYHF in the development of new Smart AI based solutions have the potential to advance research in healthcare, facilitate patient-centred innovation development, and increase the value proposition of relevant Innovative products. Ultimately, the increased use of digital health technologies, such as the STRATIFYHF and its Medical Mobile App will help to improve patient care. The current complexity of the regulatory pathways for DSS and Medical Mobile Apps in the EU is leading to Europe being less attractive to develop these innovations, whether these are used as Closed Continuous Monitoring Systems, or Predictive Tools or even in another cluster of drug development tools in clinical studies or when used together with Innovation and/or Digital Tools and / or medicinal products or investigational medicinal products for a medical purpose.

STRATIFYHF DSS and Mobile App can generate data that can be used to train AI algorithms, which will be particularly transformative in cardiovascular health-care delivery. However, digital and health-care data repositories used to train AI algorithms can introduce bias when data are homogeneous and health-care processes are inequitable. AI bias can also be introduced during algorithm development, testing, implementation, and post-implementation phases. The consequences of AI algorithmic bias can be considerable, including missed diagnoses, misclassification of disease, incorrect risk prediction, and inappropriate treatment recommendations. This bias can disproportionately affect marginalised demographic groups. In this deliverable, we provide a brief overview of AI applications in cardiovascular health care, discuss stages of algorithm development and associated sources of bias, and provide examples of harm from biased algorithms. We propose strategies that can be applied during the training, testing, and implementation of AI algorithms to mitigate bias so that all those at risk for or living with cardiovascular disease might benefit equally from AI[36].

Time constraints in primary care contribute to the low concordance for final diagnosis. One-third of primary care physicians are dissatisfied with the time available per patient and suggest this compromises the care they provide[37]. Under time pressure, primary care physicians were reported to ask significantly fewer questions and conduct less thorough clinical examinations[38].

Furthermore, studies indicate that despite a growing abundance of disease-specific guidelines, they are frequently not applied, resulting in unnecessary diagnostic tests and inadequate or potentially harmful

[36] *Mitigating the risk of artificial intelligence bias in cardiovascular care, Mihan, Ariana et al. The Lancet Digital Health, Volume 6, Issue 10, e749 - e754*

[37] *Irving G, et al. International variations in primary care physician consultation time: a systematic review of 67 countries. BMJ Open. 2017;7:e017902. doi: 10.1136/bmjopen-2017-017902.*

[38] *Tsiga E, Panagopoulou E, Sevdalis N, Montgomery A, Benos A. The influence of time pressure on adherence to guidelines in primary care: an experimental study. BMJ Open. 2013;3:e002700. doi: 10.1136/bmjopen-2013-002700.*

treatments[39]. An estimated 30–40% of patients receive non-evidence-based treatments, of which 20–25% are not needed or are potentially harmful[40].

DSS are defined as any electronic system designed to directly aid clinical decision-making that can help generate patient-specific assessments or recommendations, which are presented to clinicians for consideration[41]. Previous studies on other health conditions, such as gastrointestinal disease and critical care, have suggested that DSS can result in significantly safer prescribing decisions and closer adherence to recommended guidelines compared to their peers using paper resources[42]. The World Health Organization (WHO) has identified the development of health information systems and digital technologies, including CDSS, as one of the priorities to strengthen PHC[43]. However, research such as the one implemented by STRATIFYHF on effective and applicable approaches to utilize CDSS to strengthen PHC remains scarce[44].

The main outcomes of interest will be patients' or clients' health outcomes, to be assessed through validated measures; providers' use and adherence to recommendations, guidelines, or protocols (e.g. appropriate referrals, management); time and test efficiency and diagnostic accuracy or concordance between the CDSS diagnosis and final diagnosis.

Other outcomes of interest should include physicians' acceptability and satisfaction with the intervention; patients' or clients' acceptance of and satisfaction with the intervention; economic evaluations; reports of impact on resource use; quality of data, and unintended consequences.

Health system-wide factors were found to impact DSS success. Time constraint is one of the main barriers to DSS being used in clinical practice, despite the intention that DSS achieve time efficiency. Studies showed potential time savings with DSS use, and while one reported longer visits, it would be possible to employ a DSS in consultations lasting a competitive time frame, which would be beneficial to all parties involved. The use of DSS and Medical Mobile Apps by allied health professionals, as well as doctors, should aim to improve clinical outcomes, thus not necessarily extending consultation time.

3.3.1 AI as a catalyst for empathy and efficiency

AI has the potential to restore empathy in clinical practice by reducing administrative burden and enabling more meaningful patient interactions[45]. Most clinicians nowadays have experienced utilizing ambient AI-powered tools that transcribe meeting notes during consultations and how it has allowed them to focus on direct communication and establish stronger connections with his patient. They all envision similar applications in clinical settings where AI could handle documentation while clinicians concentrate on interactions with patients, "bringing back humanity" to the consulting room.

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[39] Sunjaya AP, Martin A, Jenkins C. Co-designing a primary care breathlessness decision support system: general practitioners requirements analysis, workflow assessment and prototype development. Stud. Health Technol. Inf. 2021;279:149–156. doi: 10.3233/SHTI210103.

[40] Fischer F, Lange K, Klose K, Greiner W, Kraemer A. Barriers and strategies in guideline implementation-a scoping review. Healthcare (Basel) 2016;4:36. doi: 10.3390/healthcare4030036.

[41] Bright TJ, et al. Effect of clinical decision-support systems: a systematic review. Ann. Intern. Med. 2012;157:29–43. doi: 10.7326/0003-4819-157-1-201207030-00450.

[42] Mickan S, Atherton H, Roberts NW, Heneghan C, Tilson JK. Use of handheld computers in clinical practice: a systematic review. BMC Med. Inf. Decis. Mak. 2014;14:56. doi: 10.1186/1472-6947-14-56.

[43] Binagwaho A, Adhanom Ghebreyesus T. Primary healthcare is cornerstone of universal health coverage. BMJ. 2019;365:l2391. doi: 10.1136/bmj.l2391.

[44] Langlois EV, Barkley S, Kelley E, Ghaffar A. Advancing the science and practice of primary health care as a foundation for universal health coverage: a call for papers. Bull. World Health Organ. 2019;97:515–515A. doi: 10.2471/BLT.19.239889.

[45] Spear, J. et. al.. (2023). Applications of Artificial Intelligence in Health Care Delivery. Journal of medical systems, 47(1), 121.

3.3.2 Personalizing risk assessment: The future of decision support

Looking ahead, STRATIFYHF discusses how innovative decision support tools under development can personalize risk assessment for patients. Unlike traditional population-based metrics, such tools iteratively evaluate individual risks and incorporate patient preferences into their calculations, which are made dynamically.

For instance, they can allow patients to weigh outcomes like stroke, bleeding, heart attack, or even death based on individual preferences, which is fed into the calculations. Such personalized approaches are not only closer to the biological reality of humans but also reflect the evolving picture of one's health journey and represent a significant leap forward in tailoring care to individual needs.

3.3.3 Bridging science and culture

While digital health technologies hold immense promise for transforming cardiovascular and emergency care, their success hinges on addressing social and cultural challenges within healthcare systems, not necessarily creating the latest cutting-edge technologies.

"This is not the end; this is not even the beginning of the end; this is the end of the beginning." By fostering alignment among stakeholders within healthcare institutions, the true potential of today's digital solutions—the opportunities they offer to strengthen patient education, alleviate administrative tasks, and foster a closer and stronger bond between healthcare professionals and patients—may be realized.

The insights shared by PKNM Solutions might underscore the critical interplay between technology, culture, and human connection in shaping the future of medicine—one where both clinicians and patients thrive in an increasingly digital world.

4. The Artificial Intelligence

Over the last decade, software has begun to permeate and transform virtually every industry, and health care is no exception. The software that drives market disruptors, including smartphones, social media, and the sharing economy, has fundamentally changed the way we live, work, and play. It's also powering game-changing developments in exponential medicine, including 3D printing, point-of-care diagnostics, robotics, bioinformatics, synthetic biology, genomics, and more. Software is changing how clinicians practice medicine, how consumers manage their own health, and how patients and providers interact. One revolutionary development in digital health technology is software that can perform complex medical functions—software as a medical device (SaMD). SaMD can diagnose conditions, suggest treatments, and inform clinical management.

The FDA historically has regulated SaMD the same way as hardware-based medical devices, such as heart stents. However, according to the FDA's Digital Health Program, this approach is "not well suited for the faster, iterative design, development, and type of validation used for software-based medical technologies."[46] A stent, for example, remains untouched by the device maker once it's released into the market and implanted into the patient. In contrast, software developers can make continuous, post-launch changes to their products remotely. These changes may be related to security or feature updates, or product evolutions based on user data.

In another example, the Google DeepMind algorithm may soon be able to detect early signs of eye disease six months before clinicians can. And as this device is used on more people, its ability to detect abnormalities may become more precise and sophisticated, allowing even earlier detection, perhaps as much as a year before clinicians can. But there is a caveat: To update the algorithm's functionality, the device maker may need to release a product update, thus transforming the product that was previously approved by the FDA. The current regulatory process emphasizes thorough vetting before products are released into the market, without much continuous evaluation after.

Powered by AI-enabled algorithms in some instances, some SaMD can also outperform the accuracy of diagnoses by trained clinicians. In Great Britain, the National Health Service (NHS) is teaming with Google's DeepMind to help doctors spot the early signs of sight-threatening eye diseases. Google's British-based AI division will use machine learning to analyse more than one million anonymous eye scans, creating computer algorithms that can detect early warning signs that clinicians—even seasoned ones—might miss. The hope is that this collaboration may lead to earlier detection and treatment of common eye diseases such as age-related macular degeneration and diabetic retinopathy, the latter being the fastest-growing cause of blindness around the world[47].

The 2021 European Society of Cardiology guideline on diagnosis and treatment of acute and chronic heart failure (HF) and the 2023 Focused Update include recommendations on the pharmacotherapy for patients with New York Heart Association (NYHA) class II–IV HF with reduced ejection fraction. However, multinational data from the EVOLUTION HF study found substantial prescribing inertia of GDMT in clinical practice. The cause was multifactorial and included limitations in organizational resources. Digital solutions like digital consultation, digital remote monitoring, digital interrogation of cardiac implantable electronic devices, clinical decision support systems, and multifaceted interventions are increasingly available worldwide. The objectives of this Clinical Consensus Statement are to provide (i) examples of digital solutions that can aid the optimization of prescription of GDMT, (ii) evidence-based insights on the optimization of prescription of

[46] *FDA, "Digital Health Innovation Action Plan," accessed January 10, 2018, https://www.fda.gov/downloads/MedicalDevices/DigitalHealth/UCM568735.pdf.*

[47] *James Vincent, "Google DeepMind will use machine learning to spot eye diseases early," The Verge, July 5, 2016, https://www.theverge.com/2016/7/5/12095830/google-deepmind- nhs-eye-disease-detection.*

GDMT using digital solutions, (iii) current evidence gaps and implementation barriers that limit the adoption of digital solutions in clinical practice, and (iv) critically discuss strategies to achieve equality of access, with reference to patient subgroups. Embracing digital solutions through the use of digital consults and digital remote monitoring will future-proof care by enabling alerts to clinicians, for example, notifying them of patients on suboptimal GDMT. Researchers should consider employing multifaceted digital solutions to optimize effectiveness and use study designs that fit the unique sociotechnical aspects of digital solutions. Artificial intelligence solutions can handle larger data sets and relieve medical professionals' workloads, but as the data on the use of artificial intelligence in HF is limited, further investigation is warranted[48].

4.1 AI in Europe

AI algorithms can identify those at risk of CVD, allowing for early intervention to change the trajectory of the disease. However, AI bias can arise from any step in the development, validation, and evaluation of algorithms. Biased algorithms can perform poorly in historically marginalized groups, amplifying healthcare inequities based on age, sex or gender, race or ethnicity, and socioeconomic status. In this perspective, we discuss the sources and consequences of AI bias in CVD prediction or detection. STRATIFYHF considers significantly an AI health equity framework and reviews bias mitigation strategies that can be adopted during the AI lifecycle[49].

Overall, generative AI is truly transformative, giving applications ranging from the creative industries to data-driven decision-making in business.

4.2 Could Predictive AI ever become Regulated?

Predictive AI is a branch of artificial intelligence that uses historical data and statistical algorithms to forecast future outcomes or behaviours. Unlike generative AI, which creates new content, predictive AI focuses on analysing patterns and trends to make informed predictions about what might happen next.

STRATIFYHF will use Historical data to build upon its modelling Strategy and create Smart but Comprehensive AI Algorithms and have to be well aware that Predictive AI is not yet easily Regulated as per MDR and AI Act within the Lifesciences sector.

The difference between generative AI and predictive AI lies in their primary functions. While generative AI is designed to create, predictive AI is built to forecast. This distinction is crucial for businesses aiming to implement AI solutions tailored to their specific needs.

Predictive AI models work by:

- Collecting and preprocessing large amounts of historical data,
- Identifying patterns and relationships within the data,

[48] *Mark Johan Schuuring, Roderick Willem Treskes, Teresa Castiello, Magnus Thorsten Jensen, Ruben Casado-Arroyo, Lis Neubeck, Alexander R Lyon, Nurgul Keser, Marcin Rucinski, Maria Marketou, Ekaterini Lambrinou, Maurizio Volterrani, Loreena Hill, Digital solutions to optimize guideline-directed medical therapy prescription rates in patients with heart failure: a clinical consensus statement from the ESC Working Group on e-Cardiology, the Heart Failure Association of the European Society of Cardiology, the Association of Cardiovascular Nursing & Allied Professions of the European Society of Cardiology, the ESC Digital Health Committee, the ESC Council of Cardio-Oncology, and the ESC Patient Forum, European Heart Journal - Digital Health, Volume 5, Issue 6, November 2024, Pages 670–682 https://doi.org/10.1093/ehjdh/ztae064*

[49] *Mihan, A., Pandey, A. & Van Spall, H.G.C. Artificial intelligence bias in the prediction and detection of cardiovascular disease. npj Cardiovasc Health 1, 31 (2024). https://doi.org/10.1038/s44325-024-00031-9*

- Using these patterns to make predictions about future events or behaviours.

Some common predictive AI tools include:

- Regression analysis,
- Decision trees,
- Neural networks,
- Time series forecasting.

These tools enable businesses to make data-driven decisions, optimize operations, and stay ahead of market trends.

The value of **predictive AI** in strategic planning, risk reduction, and decision-making cannot be overstated. By leveraging historical data and advanced algorithms, businesses can:

- Anticipate customer needs and preferences,
- Optimize inventory management,
- Detect fraud and security threats,
- Improve financial forecasting,
- Enhance marketing campaign effectiveness.

In healthcare, predictive AI can be used to identify patients at high risk of developing certain conditions, enabling early intervention and potentially saving lives. By analysing patient data, including medical history, lifestyle factors, and genetic information, predictive AI models can flag individuals at risk of heart disease, diabetes, or other chronic conditions.

The power of predictive AI lies in its ability to process vast amounts of data and identify complex patterns that might be invisible to human analysts. This capability allows businesses to make more informed decisions, reduce uncertainty, and gain a competitive edge in their respective markets.

As we go deeper into the world of AI, it's important to understand how predictive AI differs from other forms of artificial intelligence, particularly generative AI. In the next section, we'll explore the key differences between these two powerful AI technologies and how they can be applied in various business contexts.

Key Differences Between Generative and Predictive AI

When it comes to generative vs predictive AI, it's essential to understand their unique characteristics and applications. Both types of AI have revolutionized various industries, but they serve different purposes and operate in distinct ways.

The fundamental difference between generative and predictive AI lies in their primary objectives. Generative AI is designed to create new content, while predictive AI focuses on forecasting future outcomes based on historical data.

Generative AI:

- Creates original content (text, images, audio, video),
- Synthesizes new ideas or concepts,
- Produces novel solutions to problems,
- Generates creative outputs.

Predictive AI:

- Analyses historical data to identify patterns,
- Forecasts future trends or behaviours,
- Assesses risks and probabilities,
- Provides insights for decision-making.

For instance, a generative AI system might be used to create a new marketing campaign slogan, while the opposite of generative AI, i.e., a predictive AI system, would analyse past campaign performance to forecast the success of future marketing efforts.

Data Usage:

The way these AI systems handle data is another crucial distinction. Generative AI uses data as a foundation for creating something new, while predictive AI relies on historical data to make forecasts.

Generative AI:

- Learns patterns from training data,
- Uses learned patterns to generate new, original content,
- Can create outputs that don't exist in the training data,
- Often employs techniques like GANs (Generative Adversarial Networks) or transformers.

Predictive AI:

- Analyses historical data to identify trends and patterns,
- Uses these patterns to make predictions about future events,
- Relies heavily on the quality and quantity of historical data,
- Often uses statistical models and machine learning algorithms.

For example, a generative AI system trained on a dataset of paintings could create a new, original artwork in a similar style. In contrast, a predictive AI system would analyse sales data of artworks to predict which styles might be popular in the coming months.

4.3 Main Characteristics of a Decision Support System

The prime objective of using a DSS is to access information that is easy to understand. A DSS system is helpful because of its flexibility. It can be adjusted to produce several user-specified types of reports. For example, the DSS can output generated information in a bar chart format to illustrate the written data.

With continuous technological advancements, data interpretation is no longer limited to large, bulky mainframe computers. Because a DSS is mainly an application, it can be installed on most computer systems and is suitable for desktops and laptops. There are even some DSS applications that can be used on mobile devices. The adaptability of the DSS is notably advantageous for users who may need to travel for a bit. The system allows them to stay well-informed at all times and provides them with the opportunity to make the best decisions for their patients and business on the go or even on the spot.

4.4 Trusting the truth claims made by developers

DSS developers might assume that their users are interested in the innovative machine learning or knowledge representation method used, or how many lines of code the CDSS incorporates. However, Petkus *et al*[50], a recent survey of the views and experience of 19 senior UK physicians representing the views of a variety of specialities provides some evidence of what a body of senior clinicians expect from CDSSs, which developers can use to shape their truth claims and build clinical trust. While this is not generalisable/representative of all clinicians, it does provide a useful illustration of clinical concerns, and our intent is to demonstrate how applying O'Neill's trust/trustworthiness framework[51] might help our understanding of how to mitigate these issues.

4.4.1 Developer actions that suggest competence and commitment to producing high quality clinical decision support systems (DSSs)

1. Recruit and retain a good development team with the right skills.[52]
2. Use the right set of programming tools and safety-critical software engineering processes and methods, for example, Hazard and Operability Analysis (HAZOP), to understand and limit the risks of CDSSs.[53]
3. Carry out detailed user research for example, user-centred design workshops; establish an online user community and monitor it for useful insights; or form a multidisciplinary steering group of key stakeholders.[54]
4. Obtain the best quality, unbiased data to train the algorithm; use the right training method and diagnostics to monitor the learning process.[55]
5. Implement relevant technical standards, obtain a CE mark (Conformitè Europëenne: the EU's mandatory conformity mark by which manufacturers declare that their products comply with the legal requirements regulating goods sold in the European Economic Area) for their CDSS as a medical device.[56]
6. Publish an open interface to their software; carry out interoperability testing.[57]
7. Build on a prior track record of similar products that appeared safe.[58]
8. Follow relevant codes of practice for artificial intelligence and data-based technologies.[59]
9. Implement continuing quality improvement methods, for example, log and respond to user comments and concerns[60];

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[50] *Petkus H, Hoogewerf J, Wyatt JC, et al. AI in the NHS– are physicians ready? A survey of the use of AI & decision support by specialist societies, and their concerns. Clinical Medicine 2020; 20:324–8.*

[51] *Caroline Jones , James Thornton , Jeremy C WyattArtificial intelligence and clinical decision support: clinicians' perspectives on trust, trustworthiness, and liability*Medical Law Review*, Volume 31, Issue 4, Autumn 2023, Pages 501–520, https://doi.org/10.1093/medlaw/fwad013*

[52] *FDA. Digital health software Precertification (Pre-Cert) program. from. 2020;*

[53] *Mahadevaiah G, RV P, Bermejo I, et al. Artificial intelligence-based clinical decision support in modern medical physics: selection, acceptance, commissioning, and quality assurance. Med Phys 2020; 47.*

[54] *Walsh K, Wroe C. Mobilising computable biomedical knowledge: challenges for clinical decision support from a medical knowledge provider. BMJ Health Care Inform 2020; 27.*

[55] *National Institute for Health and Care Excellence. Evidence standards framework for digital health technologies. 2019;*

[56] *EU Regulation on Medical Devices 2017/745.*

[57] *NHS Digital. Interoperability toolkit.*

[58] *FDA. Digital health software Precertification (Pre-Cert) program. from. 2020;*

[59] *UK Government Department of Health and Social Care. Code of conduct of AI and other data driven technologies. London. 2019;*

[60] *NHS Digital Clinical Safety team. DCB0129: clinical risk management: its application in the manufacture of health it systems and DCB0160: clinical risk management: its application in the deployment and use of health it systems. from. 2018;*

10. Deliver updates to the CDSS regularly[61]
11. Seek to become certified as relevant ISO compliant.

4.5 Mobile Applications in Cardiology Focusing on Heart Failure

Treatment of chronic diseases, such as heart failure, requires complex protocols based on early diagnosis; self-monitoring of symptoms, vital signs and physical activity; regular medication intake; and education of patients and caregivers about relevant aspects of the disease[62]. Smartphones and mobile health applications could be very helpful in improving the efficacy of such protocols, but several barriers make it difficult to fully exploit their technological potential and produce clear clinical evidence of their effectiveness. App suppliers do not help users distinguish between useless/dangerous apps and valid solutions. The latter are few and often characterized by rapid obsolescence, lack of interactivity and lack of authoritative information.

The WHO defines mHealth as the "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices".[63] As of January 2019, there were 5.1 billion smartphone users worldwide, equating to 67% of the population in Europe and 78% in the US, demonstrating a 4.2% growth rate in mobile connectivity compared to 2018.[64] Personal mobile devices may soon be available to most HF patients or their caregivers. The use of mHealth apps can improve education on different aspects of HF and promote the importance of self-care. Such apps can enable the patient to self-monitor symptoms and vital signs in order to actively participate in the control and management of the disease. Patients can record physical activity and daily moods, and profit from notification systems that help them keep track of medication consumption and follow the prescribed treatment plan. Cameras in mobile phones may also be used to record medical documents, for example, ECGs. Hence, mHealth apps have great potential to facilitate HF management.

HF is considered a global health care problem since it is associated with a high hospitalization rate[65], increased mortality, and impaired quality of life, leading to a heavy economic burden on global health care systems[66]. Current guidelines suggest that continuous medical therapy and patient self-care play a core role in improving the prognosis of heart failure[67]. Self-care in heart failure refers to the specific health behaviours that patients perform to manage their disease and promote health[68]. These behaviours typically include daily weight monitoring, symptom recognition, medication adherence, lifestyle changes, and regular follow-up.

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[61] *Mahadevaiah G, RV P, Bermejo I, et al. Artificial intelligence-based clinical decision support in modern medical physics: selection, acceptance, commissioning, and quality assurance. Med Phys 2020; 47.*

[62] *Andrea Mortara , Lucia Vaira , Vittorio Palmieri , Massimo Iacoviello , Ilaria Battistoni , Attilio Iacovoni , Francesca Macera , Daniele Pasqualucci , Mario Bochicchio , Renata De Maria , Would You Prescribe Mobile Health Apps for Heart Failure Self-care? An Integrated Review of Commercially Available Mobile Technology for Heart Failure Patients, Cardiac Failure Review 2020;6:e13. https://doi.org/10.15420/cfr.2019.11*

[63] *https://www.who.int/data/gho/indicator-metadata-registry/imr-details/4774*

[64] *WHO. mHealth: New Horizons for Health Through Mobile Technologies. Geneva: WHO, 2011.*

[65] *Mobile Application-Based Interventions for People with Heart Failure: A Systematic Review and Meta-Analysis, Yun-Xia Ni, Xue-Hui Liu, Li He, Ya Wen, Gui-Ying You, Journal of Nursing Management, First published: 29 July 2024, https://doi.org/10.1155/2024/6859795*

[66] *Savarese G., Becher P. M., Lund L. H., Seferovic P., Rosano G. M. C., and Coats A. J. S., Global burden of heart failure: a comprehensive and updated review of epidemiology, Cardiovascular Research. (2023) 118, no. 17, 3272–3287, https://doi.org/10.1093/cvr/cvac013.*

[67] *Heidenreich P. A., Bozkurt B., Aguilar D., Allen L. A., Byun J. J., Colvin M. M., Deswal A., Drazner M. H., Dunlay S. M., Evers L. R., Fang J. C., Fedson S. E., Fonarow G. C., Hayek S. S., Hernandez A. F., Khazanie P., Kittleson M. M., Lee C. S., Link M. S., Milano C. A., Nnacheta L. C., Sandhu A. T., Stevenson L. W., Vardeny O., Vest A. R., and Yancy C. W., 2022 AHA/ACC/HFSA guideline for the management of heart failure, Journal of the American College of Cardiology. (2022) 79, no. 17, e263–e421, https://doi.org/10.1016/j.jacc.2021.12.012.*

[68] *Evangelista L. S. and Shinnick M. A., What do we know about adherence and self-care?, Journal of Cardiovascular Nursing. (2008) 23, no. 3, 250–7, https://doi.org/10.1097/01.jcn.0000317428.98844.4d, 2-s2.0-42649119118.*

Appropriate treatment adherence and optimal self-care have positive effects on patients' outcomes (e.g., decreased mortality and improved quality of life)[69]. Despite the proven benefits of self-care, people with heart failure exhibit poor self-care behaviour[70]. Only 42% of patients persistently undertake good self-care behaviour[71]. Studies have shown that unmet needs for disease knowledge and limited access to healthcare providers are the main barriers to self-care for people with heart failure[72].

Recent advances in information technology have offered opportunities to address and resolve self-care barriers for people with heart failure. mHealth is defined as the use of mobile devices (e.g., smartphones, tablets, personal digital assistants—PDAs, and other mobile devices) to deliver health care services outside of hospital settings[73]. Mobile applications are one of the typical and popular delivery methods for mHealth worldwide[74]. Interventions based on mobile health applications have the potential to educate one one-on-one at any convenient time and place, collect real-time data, track heart failure signs and symptoms, and provide quick health advice[75].

The seven most common key features of the applications include:

1. Reminders and notifications (i.e., reminding the participants to use the application, perform self-monitoring, or take medicine);
2. Self-monitoring and assessment (i.e., conducting self-monitoring and recording vital parameters and symptoms, such as blood pressure, heart rate, and weight);
3. Goal setting (i.e., setting up a tailored goal for participants, such as physical activity);
4. Health education (i.e., providing health information or resources related to heart failure);
5. Feedback and alerts (i.e., providing clinician feedback and alerts based on physiological and symptom information);
6. Tele-coaching (i.e., providing personalized recommendations and modifying the treatment); and
7. Social interaction (i.e., access to chat rooms, discussion forums, and interactions with companions and professionals).

Notably, when delivering mobile health application-based interventions for people with heart failure, the acceptance and simplicity of use of the applications need to be considered[76], especially for elderly patients

[69] *Calero-Molina E., Hidalgo E., Rosenfeld L., Verdú-Rotellar J. M., Verdú-Soriano J., Garay A., Alcoberro L., Jimenez-Marrero S., Garcimartin P., Yun S., Guerrero C., Moliner P., Delso C., Alcober L., Enjuanes C., and Comin-Colet J., The relationship between self-care, long-term mortality, and heart failure hospitalization: insights from a real-world cohort study, European Journal of Cardiovascular Nursing. (2022) 21, no. 2, 116–126, https://doi.org/10.1093/eurjcn/zvab011.*

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[75] *Saleh Z. T, Elshatarat R. A., Elhefnawy K. A., Helmi Elneblawi N., Abu Raddaha A. H., Al-Za'areer M. S., Mofdy Almarwani A., Alzahrani N. S., Aqel A. A., Shawashi T. O., and Tayeh M., Effect of a home-based mobile health app intervention on physical activity levels in patients with heart failure a randomized controlled trial, Journal of Cardiovascular Nursing. (2023) 38, no. 2, 128–139, https://doi.org/10.1097/jcn.0000000000000911.*

[76] *Campbell G., Auyeung V., and Ismail T. F., Smartphone and email capabilities of heart failure patients, European Heart Journal-Digital Health. (2021) 2, no. 1, 5–6, https://doi.org/10.1093/ehjdh/ztab008.*

and people with limited digital literacy[77]. The characteristics of applications may reduce patient engagement and increase the attrition rate, which, in turn, affects intervention effectiveness.

4.6 Data-Driven Decisions: Enhanced Diagnosis

CVDs remain the leading cause of global mortality, as well as a substantial burden on public health worldwide necessitating advancements in diagnostic and monitoring technologies to enable timely intervention and effective management[78].. Traditional diagnostic modalities based mostly on centralized laboratory infrastructure and intermittent clinical evaluations, in most cases, hardly have the ability to aptly capture the dynamic and complex nature of cardiovascular pathophysiology[79].

HF self-management is essential to avoid decompensation and readmissions. Mobile apps seem promising in supporting heart failure self-management, and there has been a rapid growth in publications in this area. However, to date, systematic reviews have mostly focused on remote monitoring interventions using non-app types of mobile technologies to transmit data to health care providers, rarely focusing on supporting patient self-management of heart failure[80].

Despite growing interest in the use of mobile apps for heart failure self-management, critical gaps remain in their design and evaluation, with lack of patient and clinician involvement and lack of robust evaluation to determine the populations that may benefit the most. Given the importance of patient preference and engagement in the successful delivery of heart failure interventions[81], co-design processes involving clinicians and patients and process evaluations assessing engagement and acceptability of the interventions are likely to improve intervention quality and consistency[82].

Disease Diagnosis: By evaluating patient data and medical imaging, AI can help with the early diagnosis of diseases, such as cardiovascular disorders, resulting in faster and more precise diagnoses

Treatment Personalization: AI can improve patient outcomes by recommending tailored treatment plans that include medication dosages, treatments, and interventions based on analysis of patient data.

Drug Discovery: AI expedites the process of finding new drugs by detecting and forecasting prospective therapeutic candidates and their efficacious and safe profiles.

Predictive analytics: By predicting patient outcomes and identifying individuals who are more likely to develop particular medical disorders, AI enables healthcare providers to take preventative measures.

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[80] Bezerra Giordan L, Tong HL, Atherton JJ, Ronto R, Chau J, Kaye D, Shaw T, Chow C, Laranjo L. The Use of Mobile Apps for Heart Failure Self-management: Systematic Review of Experimental and Qualitative Studies. JMIR Cardio. 2022 Mar 31;6(1):e33839. doi: 10.2196/33839. PMID: 35357311; PMCID: PMC9015755.

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[82] Inglis SC, Clark RA, Dierckx R, Prieto-Merino D, Cleland JG. Structured telephone support or non-invasive telemonitoring for patients with heart failure. Heart. 2017;103(4):255–7. doi: 10.1136/heartjnl-2015-309191.heartjnl-2015-309191

Historical Development of AI in Healthcare: AI in healthcare has a long history, going all the way back to the 1960s. AI was first investigated for diagnostic purposes, but the processing capacity and data availability of early systems limited their use. AI has become more prevalent in healthcare due to technological breakthroughs such as the creation of powerful algorithms, the emergence[83] of massive data, and improved processing capacity. AI in healthcare is a rapidly developing topic that presents intriguing prospects for raising patient care standards and system efficiency.

AI has become a disruptive force in healthcare in recent years, changing how doctors identify, treat, and manage a wide range of illnesses, including cardiovascular ailments. AI, in the context of healthcare, refers to the application of algorithms and computer systems to carry out operations that have historically required human intellect. This includes a variety of technological fields such as computer vision, Natural Language Processing (NLP), deep learning, and machine learning. Together, these technologies can evaluate enormous volumes of medical data, glean insightful information, and help medical practitioners make better judgments. By enhancing diagnosis precision, forecasting illness prognoses, and customizing treatment regimens, artificial intelligence (AI) in healthcare has the potential to completely transform patient care. Artificial intelligence (AI) can help physicians make better decisions and give individualized care by sifting through massive datasets and finding trends. Healthcare workers can concentrate more on providing direct patient care by using this technology's ability to automate administrative procedures.

The integration of AI and machine learning has become indispensable for CVDs monitoring, particularly in analysing time-series data from sensors like PPG and ECG. By enabling the extraction of complex patterns and identifying anomalies indicative of potential cardiac events, AI and machine learning significantly enhance diagnostic accuracy and facilitate proactive healthcare interventions[84].

Although machine learning has great prospects for transformation, many challenges remain unresolved. Traditional machine learning models heavily depend on feature engineering, and many are not well-suited to deal with the high dimensionality and noise usually present in physiological signals. Most of the models are prone to overfitting, especially for small datasets, causing a loss of generalization and reliability during deployment in different clinical settings[85].

STRATIFYHF studies will aim to demonstrate the potential of integrating a keyword search of routinely stored electronic health records with AI-based machine learning algorithms and biobank resources for identifying heart failure (HF) subtypes. While STRATIFYHF approach shows promise in enhancing the efficiency and speed of patient selection for pragmatic clinical trials, as well as in improving HF surveillance and early diagnosis across hospital systems, it is important to acknowledge the challenges posed by limited data availability. The effectiveness of this method, particularly in terms of early disease detection and its capability to increase the availability of biomarkers and echocardiographic parameters, remains an area for further exploration. Consequently, while STRATIFYHF findings might be encouraging, they might also underscore the necessity of further studies to assess the diagnostic effectiveness of this approach fully.

[83] *https://www.researchgate.net/publication/378978484 DATA DRIVEN HEARTS - AI and ML in CARDIOVASCULAR CARE Book, December 2023*

[84] *Q. Tang, Z. Chen, Y. Guo, Y. Liang, R. Ward, C. Menon, M. Elgendi Robust reconstruction of electrocardiogram using photoplethysmography: a subject-based model Front. Physiol., 13 (2022), 10.3389/fphys.2022.859763*

[85] *R. Tripathy, M.R.A. Paternina, J. De La O Serna Editorial: machine learning and deep learning for physiological signal analysis Front. Physiol., 13 (2022), 10.3389/fphys.2022.887070*

4.7 Risk Prediction and Stratification through AI

HF is a chronic disease with high prevalence, morbidity, and mortality. The impact of HF is expected to increase substantially with the ageing of the population[86]. The overall economic cost of HF in 2012 was estimated at $108 billion per annum based on a study of the patient population across the globe[87]. With an ageing, rapidly expanding and industrializing global population, this value will continue to rise. Considering the increasing economic burden of HF, early identification of patients at increased risk of clinical deterioration and hospitalization, even prior to the development of severe symptoms, may provide an opportunity for early intervention that can prevent worsening of symptoms, slow down disease progression, and improve patient outcomes[88].

Despite high expectations for AI in medicine, translating ML models from EHRs to real-life clinical practice has faced obstacles[89].

Accessible strategies for risk stratification for HF remain elusive despite the availability of evidence-based therapies that can effectively modify the disease trajectory[90].

The gap between model development and deployment arises from model flaws, logistical challenges, lack of multi-disciplinary co-operation, insufficient implementation infrastructure, privacy and sociocultural issues, and the need for ongoing model assessment and financial support. Some authors compare translational ML with drug discovery, requiring further validation in clinical trials. While we agree with previous authors that external validation of data is necessary, it should be conducted by independent authors, where feasible, to avoid publication and reporting bias.

The use of cutting-edge technologies in rapid testing and continuous monitoring for CVDs is indeed among the most prestigious developments in modern healthcare. As such, it has brought unprecedented accuracy and speed to diagnosis, monitoring, risk prediction and stratification.

EHR linked to DICOM, biological specimens, and Deep Learning (DL) algorithms could potentially improve patient care through automated case detection and surveillance[91].

AI and machine learning help in the fast testing and early prediction of CVDs by enabling advanced signal processing and feature extraction from PPG and ECG data. The advancement from traditional machine learning to sophisticated deep learning architectures has largely improved the functionality of CVDs

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[86] *Heidenreich PA, Fonarow GC, Opsha Y, Sandhu AT, Sweitzer NK, Warraich HJ, et al. Economic issues in heart failure in the United States. J Card Fail 2022; 28: 453–466.*

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[89] *Ammar Zaka, Daud Mutahar, James Gorcilov, Aashray K Gupta, Joshua G Kovoor, Brandon Stretton, Naim Mridha, Gopal Sivagangabalan, Aravinda Thiagalingam, Clara K Chow, Sarah Zaman, Rohan Jayasinghe, Pramesh Kovoor, Stephen Bacchi, Machine learning approaches for risk prediction after percutaneous coronary intervention: a systematic review and meta-analysis,* European Heart Journal - Digital Health*, Volume 6, Issue 1, January 2025, Pages 23–44, https://doi.org/10.1093/ehjdh/ztae074*

[90] *Shahim B, Kapelios CJ, Savarese G, Lund LH. Global public health burden of heart failure: An updated review. Card Fail Rev. 2023;9. doi: 10.15420/cfr.2023.05*

[91] *Artificial intelligence-assisted automated heart failure detection and classification from electronic health records, Mon Myat Oo, Chuang Gao, Christian Cole, Yoran Hummel, Magalie Guignard-Duff, Emily Jefferson, James Hare, Adriaan A. Voors, Rudolf A. de Boer, Carolyn S.P. Lam, Ify R. Mordi , First published: 03 May 2024, https://doi.org/10.1002/ehf2.14828*

monitoring systems by surmounting the previous limitations and thus paving the way for more accurate, reliable, and personalized cardiac healthcare solutions[92].

The prediction of cardiac disease helps practitioners make more accurate decisions regarding patients' health. Therefore, the use of Machine Learning (ML) is a solution to reduce and understand the symptoms related to heart disease[93].

The growth in medical data collection presents a new opportunity for physicians to improve patient diagnosis. In recent years, practitioners have increased their usage of computer technologies to improve decision-making support[94]. In the healthcare industry, machine learning is becoming an important solution to aid in the diagnosis of patients[95]. ML is an analytical tool used when a task is large and difficult to program, such as transforming medical record into knowledge, pandemic predictions, and genomic data analysis[96].

Clinical decision support systems can be incorporated with ML algorithms to aid healthcare professionals in making informed decisions. Based on the analysis of existing or on-going data collection, these systems can provide real-time feedback, generate automated reports, and recommend additional diagnostic tests or treatment options[97].

STRATIFY HF will aim to develop a score, which could assist on triaging HF risk score by providing sensitive and specific multi-parameter (s) integrated diagnostic measure (s) that predicted the occurrence of HFEs in an unselected, large patient sample size and to be validated as per its predictive accuracy in a real-world population. The STRATIFY HF risk score will retain its accuracy in the presence of co-morbidities that alter risk prediction. This STRATIFYHF risk score will be an assistive tool to predict, somehow realistically, the rate of all-cause mortality.

Identifying individuals most likely to develop future HF can alleviate these risks with early initiation of low-cost medical therapies that have been proven in clinical practice guidelines to modify the trajectory of the disease, reducing both the risk for incident clinical HF and improving life expectancy[98].

[92] *O. Patrascanu, D. Tutunaru, C. Musat, O.Dragostin, A. Fulga, L. Nechita, A. Ciubară, A. Piraianu, E. Stamate, D.G. Poalelungi, I.Drag ostin, D. Iancu, A. Ciubară, I. Fulga Future horizons: the potential role of artificial intelligence in cardiology J. Personalized Med., 14 (2024), 10.3390/jpm14060656*

[93] *Anna Karen Gárate-Escamila, Amir Hajjam El Hassani, Emmanuel Andrès, Classification models for heart disease prediction using feature selection and PCA, Informatics in Medicine Unlocked, Volume 19, 2020, 100330, ISSN 2352-9148,, https://doi.org/10.1016/j.imu.2020.100330. (https://www.sciencedirect.com/science/article/pii/S2352914820300125)*

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[95] *T. Hastie, R. Tibshirani, J. Friedman, The elements of statistical learning: data mining, inference, and prediction Springer (2017)*

[96] *S. Marsland Machine Learning: an algorithmic perspective CRC Press, Boca Raton, FL (2015)*

[97] *Review Article, Free Access, Artificial intelligence and heart failure: A state-of-the-art review, Muhammad Shahzeb Khan, Muhammad Sameer Arshad, Stephen J. Greene, Harriette G.C. Van Spall, Ambarish Pandey, Sreekanth Vemulapalli, Eric Perakslis, Javed ButlerFirst published: 10 August 2023, https://doi.org/10.1002/ejhf.2994*

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5. Regulatory Context and Scope

EU AI ACT as the most relevant AI Regulatory framework along with the MDR as per STRATIFYHF potential innovation outcomes (DSS & Medical Mobile App) require Risk based development to reach Regulatory clearances, upon successful Verification and Validation processes. These are classified into different risk categories based on criteria such as their application and target audience. The legislative norms then define measures that companies using or selling AI systems must implement, depending on the risk category. Required measures range from a simple disclosure obligation for low-risk applications (e.g., chatbots in customer service) to extensive documentation and duty of care for high-risk applications (e.g., applications used in HR) to a complete ban on prohibited applications or those posing an unacceptable risk (e.g., social scoring or systems attempting to subliminally manipulate the behaviour of children or individuals with intellectual disabilities).

The Regulations dedicated to AI aim to enhance the national and global market and promote trustworthy AI systems by protecting fundamental rights and addressing potential harmful effects while supporting innovation.

The AI Regulations are applicable to all providers that make an AI system or general-purpose AI model available on the global market, regardless of where the company is based. Scientific purpose only, and Military and National security AI systems are excluded from the regulation.

Classification of the AI systems follows, as appropriate, a risk-based approach to AI regulations, categorizing AI systems into 4 different risk levels as depicted in **Figure 2** below:

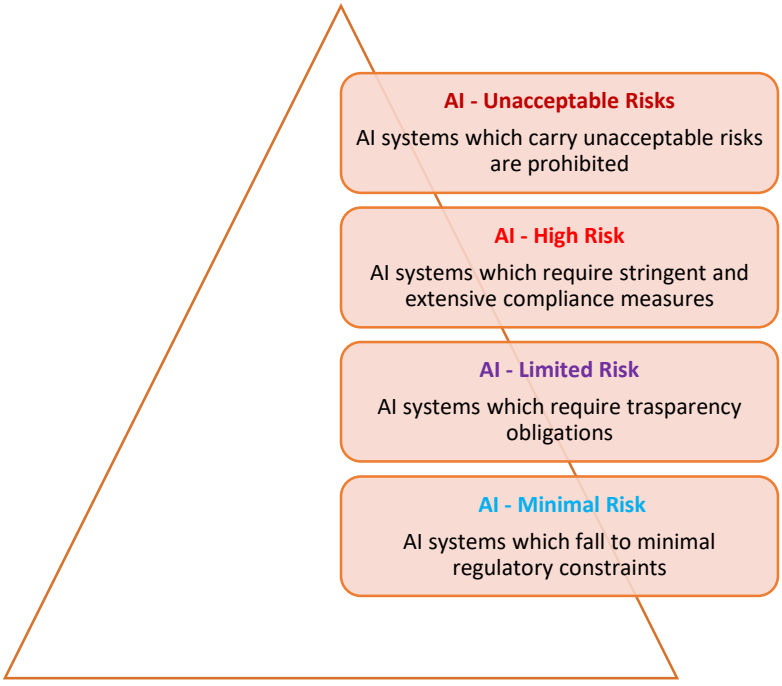

Figure 2. Risk-based approach of the AI systems classification

Medical AI devices predominantly fall under the high-risk category, subjecting them to:

– Comprehensive risk management systems,

– Rigorous conformity assessments,

– Detailed documentation requirements,

– Ongoing monitoring and reporting obligations.

AI medical device providers will face demanding, new global regulatory requirements:

– New notification obligations,

– Additional conformity assessment,

– Complex compliance and verification testing,

More particularly, the following issues will be of specific concern:

Human oversight: AI systems must be overseen by qualified employees within the company who have appropriate training and authority.

Data quality: Deployers must ensure input data is relevant for its designated purpose.

Data protection assessment: AI deployers must conduct data protection impact assessments before placing any AI system into service.

Record keeping: AI systems deployers or developers must maintain the automatically generated logs.

Transparency: The use of AI systems needs to be communicated to the device users.

Instructions for use: AI systems developers need to include additional information on the capabilities and limitations of the systems, and descriptions of the mechanisms.

System monitoring: Incidents related to AI systems must be reported.

Risk Assessment: AI system developers must identify additional risks, such as threats to health, safety or fundamental rights.

5.1 Framework for Regulatory Assessment

The global medical devices and AI regulatory framework constitutes a comprehensive system of rules and regulations designed to harmonize laws across IMDRF member states, in order to promote the easier movement of goods and services, protect consumers, and ensure fair competition. It encompasses various areas like information security, IT and telecommunications, energy, environment, and end-user protection. This framework includes directives, regulations, and decisions that establish the legal basis for the above-mentioned sectors.

A competitive regulation agenda helps the global market with evidence-based policies and laws that achieve their objectives in the most efficient way, while being tailored to the needs of end-users (patients), businesses, and civil society. The following figure (**Fig.3**) represents the initiative of the regulatory authorities to develop simple and better legislative norms based on evidence-based actions, which involve all the relevant stakeholders such as manufacturers, patients, medical practitioners, decision makers, competent authority and policy makers. As a principle, better regulation, which includes guidelines and toolboxes provide concrete guidance to the regulatory bodies involved in preparing new initiatives and proposals or managing and evaluating existing legislation.

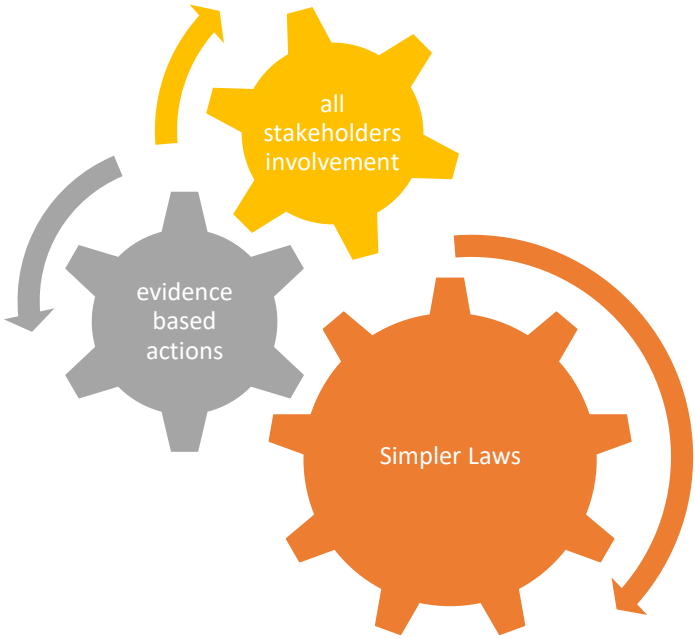

Figure 3. Global Regulatory Authorities' intention

More particularly, better regulation ensures that:

- Global Regulatory actions are **informed by the best available evidence** and designed to achieve the desired impact to bring benefits for the global society, economy and environment
- The decision-making is intended to be **open and transparent** for citizens, businesses and other stakeholders

Citizens and stakeholders are allowed to **contribute** to the policy and law-making process through stakeholders' consultations, online public consultations, implementation dialogues, reality checks and feedback processes.

5.2 European Regulatory Landscape

Currently, in Europe, there are no laws or harmonized standards that specifically regulate the use of AI in medical devices. However, it appears that these devices must comply with existing regulatory requirements such as MDR and IVDR, e.g.:

- Manufacturers must demonstrate the **benefits** and **performance** of the medical devices. For example, devices used for diagnosis require proof of diagnostic sensitivity and specificity.
- The MDR requires manufacturers to ensure the **safety** of devices. This includes ensuring that software is designed to ensure **repeatability, reliability, and performance** (see MDR Annex I, 17.1 or IVDR Annex I, 16.1).
- Manufacturers must formulate a precise **intended purpose** (MDR/IVDR Annex II). They must validate their devices against the intended purpose and stakeholder requirements and **verify** them against the specifications (including MDR Annex I, 17.2 or IVDR Annex I, 16.2). Manufacturers are also required to describe the methods they use to provide this evidence.

- If the **clinical evaluation** is based on a comparative product, there must be **technical equivalence**, which explicitly includes the evaluation of the software algorithms (MDR Annex XIV, Part A, Paragraph 3). This is even more difficult in the case of performance evaluation of in vitro diagnostic medical devices (IVDs). Only in well-justified cases can a clinical performance study be waived (IVDR Annex XIII, Part A, Paragraph 1.2.3).

The AI Act applies to most medical and IVD medical devices that use artificial intelligence procedures, particularly machine learning. If a notified body is to be involved in the conformity assessment for these devices, i.e., if the devices do not fall into the lowest class, then they are even considered "high-risk devices" under the AI Act.

Nevertheless, AI medical devices will require a new certification under the AI Regulations in addition to the CE certification under Regulation EU 2017/745 and 2017/746 (MDR/IVDR).

At a glance, it is expected that most Notified Bodies will be authorized under the AI Act and therefore will be able to certify medical devices under both the AI Act and MDR/IVDR regulations concurrently. In addition, similar to the implementation of MDR and IVDR, some delays in the availability of authorized NBs are to be expected.

The registration of such products has to fulfil MDR/IVDR requirements accordingly through the EUDAMED registration. More particularly, before putting a medical device with a high-risk AI system on the market or into service, the provider or, where applicable, the authorized representative, is expected to register themselves and their system in the EU AI database, when available. This is similar to EUDAMED system where basic information about the high-risk AI system and its provider would be listed.

The timeline of the EU AI Act implementation is defined in the figure below:

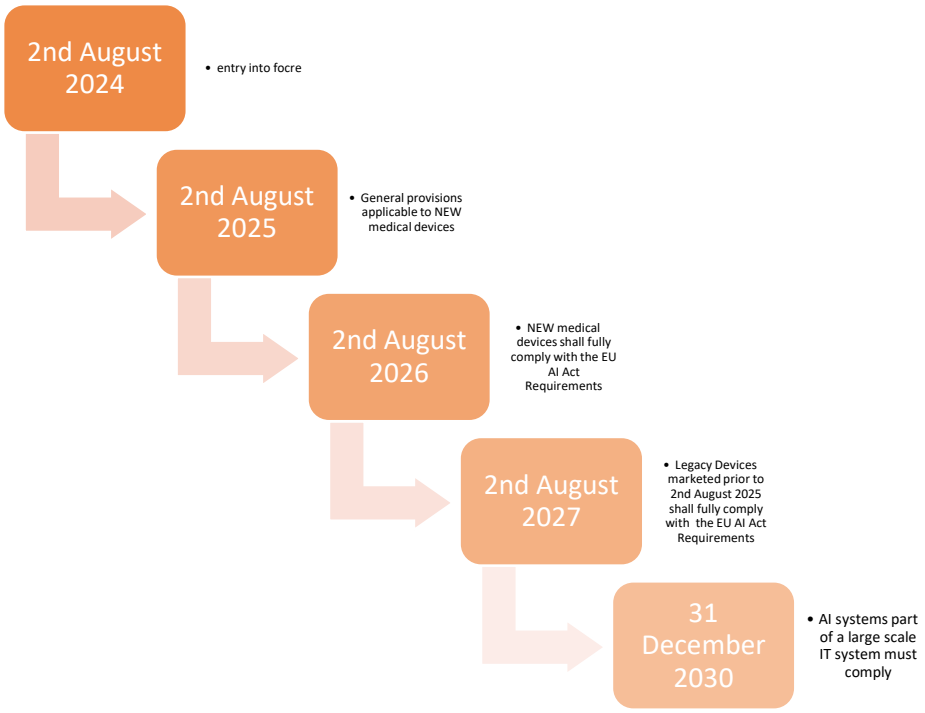

Figure 4. Implementation Timeline of the EU AI Act[99]

[99] *https://artificialintelligenceact.eu/implementation-timeline/*

Concerning the realistic impact of the EU AI Act, AI medical device providers will face demanding new regulatory requirements in the EU, although the Global concern is to facilitate products into the market and make the regulations easier. The manufacturers of AI medical device systems will face:

- New notification obligations,
- Additional conformity assessment,
- Complex compliance and verification testing.

Concerning the Regulatory Framework of the future products, as per their intended purpose and independently of the AI modules, for both DSS and Medical Mobile app, the EU's MDR (Medical Device Regulation) and EU AI Act shall apply.

In essence, both STRATIFYHF DSS and Mobile app, particularly are subject to various regulatory frameworks to ensure they are safe, effective, and compliant with data privacy and security regulations.

5.3 The U.S. approach

Similarly to the EU, the 21st Century Cures Act (Cures Act) and its subsequent implementation by the FDA, including the clarification of medical software regulation, has a risk-based approach to the regulation of medical U.S. FDA: The FDA regulates medical devices, including CDSS, to ensure safety and efficacy. It also regulates mobile apps that are considered medical devices.

Generally, the FDA may require premarket review for certain medical devices, including those with higher risk levels, according to the agency's guidelines, and **it** monitors medical devices after they are on the market to ensure they continue to meet safety and efficacy standards.

The **US Federal Trade Commission (FTC)** enforces laws related to data privacy and protection, including those that apply to mobile apps and data collection. The FTC also investigates and takes action against unfair or deceptive practices in the marketing and use of mobile apps. Various international and state laws, such as the California Consumer Privacy Act (CCPA) and New York's Health Cloud Act, regulate the collection and use of personal data. These laws also address data security measures to protect patient data from unauthorized access and disclosure.

Additionally, HL7 develops standards for the exchange of health information, including EHRs, while SNOMED CT is a standardized coding system for medical terminology, used to ensure consistency in data exchange. DICOM provides standards for the exchange of medical images. At last, the initiative of the **United States Core Data for Interoperability** standards for data elements, such as lab results, medications, and patient demographics, according to the CDC.

The number of clinical AI algorithms cleared by the U.S. Food and Drug Administration (FDA) is on track to surpass 1,000 before the end of 2024.

Cardiology remains the No. 2 speciality with the most AI algorithms, according to the FDA's most recent AI update released Aug. 7.

The FDA is providing this list of AI/ML-enabled medical devices marketed in the United States as a resource to the public about these devices and the FDA’s work in this area. The devices in this list have met the FDA’s applicable premarket requirements, including a focused review of the devices’ overall safety and effectiveness, which includes an evaluation of appropriate study diversity based on the device’s intended use and technological characteristics.

https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medicaldevices?utm_medium=email&utm_source=govdelivery

At its current rate, the number of clinical algorithms cleared by the FDA will break 1,000 before the end of 2024. The total sat at 950 as of the end of June. This includes 61 new approvals since the last FDA update from March. Cardiology added 13 new algorithms during that time.

Overall, cardiology now has 135 FDA-cleared AI models, 14.2% of the total number of approved algorithms.

Radiology, which had 44 new approvals since the previous update, accounts for the largest number of AI approvals from the FDA. Radiology now makes up about 76% of the 950 algorithms cleared so far. The third closest speciality for AI is neurology, with 34 algorithms, or about 3.5% of the AI clearances.

According to the risk of SaMD, the FDA classifies devices into three distinct classes (Class I low-risk devices, Class II moderate-risk devices, and Class III high-risk devices) and regulates them accordingly. The higher the risk, the stricter the control. Most of the Class I devices and all Class II devices are regulated by the FDA through the Pre-Market Notification (PMN) pathway (commonly known as 510(k) application). This is an expedited pathway that allows for devices to obtain marketing authorization if the sponsor can demonstrate substantial equivalence to an existing legally marketed device. Class III devices are devices involving the greatest risk and, therefore, are regulated by the FDA through the more stringent Pre-Market Approval (PMA) pathway.

This pathway requires extensive scientific evidence, including technical, non-clinical laboratory, and clinical investigations to demonstrate a device's safety and effectiveness prior to FDA approval. The FDA also has another pathway, De Novo pre-market review, for new low-to-moderate-risk devices without an equivalent predicate device. The De Novo pathway provides an opportunity to reclassify a novel Class III device to a Class I or Class II device, which are then subject to less stringent regulation.

5.4 FDA *vs*. CDS Functionalities

Like the FDA, the MDR has leveraged the IMDRF risk-based framework for medical device software classification. Still, the MDR is more stringent: all software functionalities that are classified as class I devices under FDA regulation, and are classified as at least class IIa devices under MDR regulation. The previous example of CDS for drug-drug interaction screening that is exempted from the Cures Act is at least classified as class IIa medical software in the EU's MDR. Since the application is used to guide the patient's treatment, it will either belong to class IIa, IIb or III depending on how developers describe and notified bodies evaluate the intended use. Not detecting a drug-drug interaction may have no consequences, but can also result in adverse drug events and, in the worst case, even death. The highest potential risk will determine the risk profile. However, the risk-based categorization seems not fully defined, thereby creating an opportunity for subjective interpretation.

Nonetheless, the FDA and the EU MDR differ significantly in their approaches to Clinical Decision Support (CDS) functionalities, particularly concerning device classification and regulatory oversight. The FDA focuses on a risk-based approach, with a tiered classification system (Class I, II, and III). The FDA's CDS Draft Guidance, based on the 21st Century Cures Act, excludes certain software functions from device definition. Conversely, the MDR classifies devices using a rules-based framework, including those with CDS functionalities. The MDR emphasizes a higher level of regulatory oversight for all medical devices, including those with CDS, regardless of risk level.

The **Table 1** below depicts a comparison between the two regulatory schemes.

Table 1. CDS Functionalities in FDA *vs*. EU MDR

FDA CDS Functionalities:	EU MDR CDS Functionalities:
Risk-Based Approach: **The FDA classifies CDS functionalities based on their risk level.**	**Rules-Based Classification:** The MDR uses a rules-based framework to classify all medical devices, including those with CDS.
Cures Act Exclusion: **The 21st Century Cures Act provides certain exemptions for software functions that meet specific criteria, effectively excluding them from being considered a medical device.**	**Higher Regulatory Oversight:** The MDR applies a higher level of regulatory oversight to all medical devices, including CDS functionalities, regardless of their risk level.
Focus on Higher-Risk CDS: **The FDA prioritizes regulatory oversight for CDS functions that inform clinical management for serious or critical conditions.**	**Clinical Evaluation:** The MDR requires a clinical evaluation for all medical devices, including those with CDS functionalities, regardless of the risk level.
Emphasis on Transparency: **The FDA requires manufacturers to describe the underlying data and rationale used by CDS algorithms, ensuring transparency.**	**Stringent Requirements:** The MDR sets stringent requirements for manufacturers, including notified bodies, to ensure compliance and market access.

The **Fig. 5** below illustrates the key differences between FDA and EU MDR to the regulatory approach of the CDS.

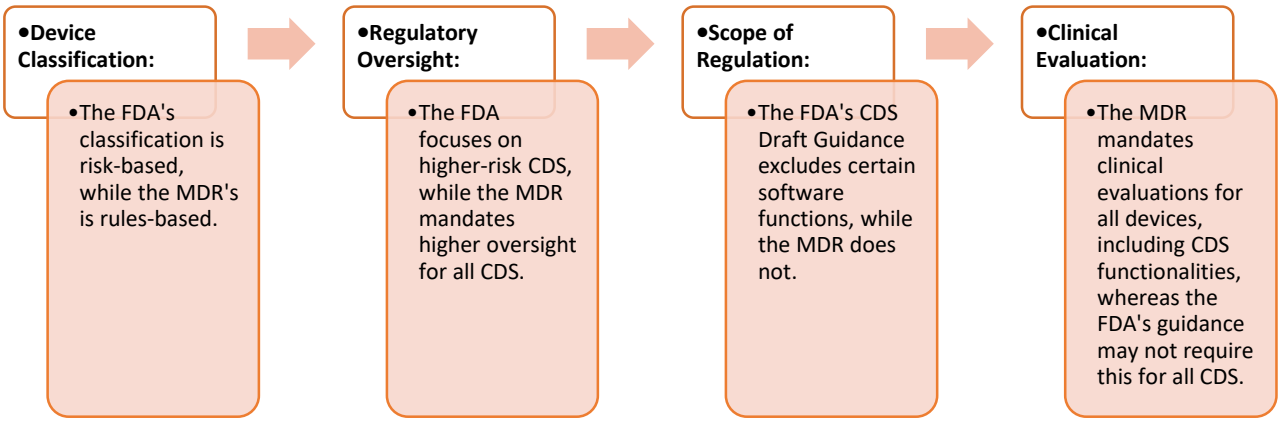

Figure 5. Schematic Representation of the key differences between EU and FDA regulatory approaches for CDSs.

In essence, the FDA's approach to CDS is more risk-based and focused on specific high-risk functions while the MDR's approach is more comprehensive and applies higher regulatory oversight to all CDS functionalities, regardless of their risk level.

5.5 Apps as Medical Devices: A Continuous Debate

The question of whether and when apps should be considered medical devices is a subject of ongoing debate, particularly in light of the increasing integration of technology into healthcare. This debate revolves around defining the line between general health and wellness apps and those that provide diagnostic or therapeutic functions, which would qualify them as medical devices subject to stricter regulations. The regulatory landscape is also complex, with different jurisdictions and organizations having varying approaches to classifying and regulating apps as medical devices.

At this stage, the Definition of a Medical Device should be considered as follows:

"*A medical device is generally defined as an instrument, apparatus, appliance, software, or other item used to diagnose, treat, mitigate, or prevent disease or injury. This definition can encompass a wide range of technologies, including mobile apps.*[100]"

In different regulatory systems, several factors are considered when classifying an app as a medical device, including its intended purpose, the level of risk associated with its use, and the specific functions it performs. For example, an app that directly diagnoses a disease or prescribes a treatment would likely be considered a medical device, while an app that provides general health information or fitness tracking might not.

Another significant issue is that the regulatory landscape for medical devices varies significantly between countries and regions, although most of them (if not all) use a risk-based approach to regulate medical devices. In some jurisdictions, like the EU, there are specific regulations for software as a medical device (SaMD), which may require approval from external designated bodies (Notified Bodies).

Several challenges and considerations surround the regulation of apps as medical devices, including the rapid evolution of technology, the difficulty in accurately assessing the risk associated with certain apps, and the need for clear and consistent regulations across different jurisdictions. In addition, the development of apps by "citizen developers" may raise concerns about the lack of formal development processes and quality control[101].

5.5.1 What Level of Evidence is Needed to Assess the Value of mHealth Apps?

Different approaches may be used to adequately assess the value of mHealth apps. As a principle, a multi-faceted approach is needed, incorporating both objective measures and subjective user feedback.

While randomized controlled trials (RCTs), known as Clinical Investigations, provide the strongest evidence, they are not always feasible or applicable to all mHealth interventions. Other methods may include systematic reviews and meta-analyses, User experience and evaluations (usability studies), Patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs), Quality assessment tools, cost-effective analysis, and Interoperability Assessments. By combining these methods, a more comprehensive understanding of an mHealth app's value can be achieved. The specific level of evidence needed will depend on the app's intended use and the specific outcomes being evaluated.

The **Fig. 6** reflects a schematic representation, which describes, a at glance, the additional evidence to be used in Mobile Apps clinical evaluation:

[100] https://www.ema.europa.eu/en/human-regulatory-overview/medical-devices
[101] https://pmc.ncbi.nlm.nih.gov/articles/PMC7252987/

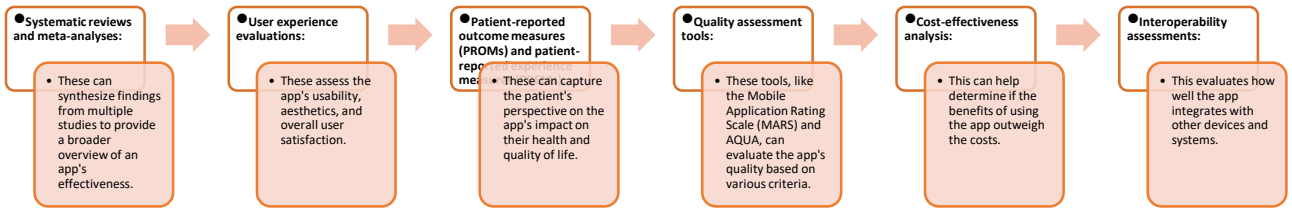

Figure 6. Schematic representation of alternative sources to clinical evidence in Mobile Apps.

6. STRATIFYHF Envision in Cardiac Care

AI in the context of STRATIFYHF holds significant promise for improving HF care, particularly in diagnosis, risk stratification, and treatment optimization. The CDSS and Mobile App AI algorithms will be able to analyse vast amounts of data, including medical images, ECGs, and electronic health records, to assist clinicians in making more accurate and timely decisions.

This will allow STRATIFYHF future products to lead to earlier detection of HF, better identification of patients at high risk, and more personalized treatment plans.

Here is a more detailed look at how STRATIFYHF plans to elaborate how AI is being used and how it is expected to evolve in heart failure care:

1. Diagnosis and Early Detection:

- **AI-powered image analysis:** STRATIFYHF AI algorithms will be able to analyse cardiac images (echocardiograms, CT scans, MRIs) to automate measurements, identify subtle abnormalities, and detect HF earlier than traditional methods, potentially leading to earlier interventions.
- **ECG analysis:** STRATIFYHF AI algorithms will analyse ECG data to identify patients at risk of HF, predict disease progression, and even identify specific types of HF (e.g., HFrEF or HFpEF).
- **Integrating diverse data:** STRATIFYHF AI algorithms will integrate data from multiple sources, like electronic health records, wearable sensors, and imaging, to create a more comprehensive picture of a patient's condition.

2. Risk Stratification and Prediction:

- **Predictive models:** STRATIFYHF aims to build models that predict the likelihood of developing HF or experiencing adverse outcomes based on a patient's individual characteristics and data.
- **Identifying high-risk patients:** These models will help identify individuals at high risk of developing HF, enabling earlier intervention and potentially preventing more severe complications.

3. Treatment Optimization and Personalization:

- **Predicting treatment response:** The AI in STRATIFYHF future products will be able to analyse data to predict how patients might respond to specific treatments, allowing clinicians to tailor treatment plans more effectively.
- **Optimizing medication regimens:** The AI algorithms of STRATIFYHF will help optimize medication dosages and combinations based on individual patient characteristics and response to therapy.
- **Remote monitoring and home care:** The Mobile App can detect early signs of worsening HF, enabling timely interventions and preventing hospitalizations.

4. Challenges and Future Directions:

- **Data privacy and security:** Ensuring the privacy and security of patient data is crucial when using AI in healthcare; this has already been considered into the Design of the CDSS and the Mobile App throughout their design process.
- **Algorithmic bias and fairness:** Software requirements include provisions for fair or accurate predictions for HF patients.

- **Interoperability and integration:** Integrating STRATIFYHF AI tools into existing healthcare systems and workflows requires careful planning and coordination.

In conclusion, STRATIFYHF is poised to transform heart failure care by enabling earlier diagnosis, more accurate risk assessment, personalized treatment plans, and improved patient management.

7. Deviation from the work plan

There is no deviation from the work plan. This deliverable will be delivered as intended.

8. Conclusions

AI may lack the empathetic understanding that human practitioners offer. While AI is excellent at analysing data, it cannot replicate the warmth and personalized care that comes from a human healthcare provider.

Some of the major challenges and risks associated with AI that STRATIFYHF should consider include:

- Biased data and functional issues,
- Black-box reasoning,
- Automation bias,
- Data privacy and security,
- Patient expectations,
- Medical practitioner training and education.

The healthcare sector generally faces many hurdles when adopting AI. Obstacles include setting an AI strategy, dealing with fragmented data, and addressing ethics, security and compliance.

One of the downsides of AI is the absence of an emotional bond between the health professional and the patient. The harmonious doctor–patient relationship plays a vital role in the attainment of treatment and healing, thus it is considered a keystone of care!

AI systems are efficient, but they can make mistakes. This causes concern. It's also hard to trust AI systems because their decision-making processes are only sometimes transparent. They require clinical validation based on the state of the art, imposing clinical investigations, which may require enormous subjects' enrolment and difficult study design.

Data bias, in other words, incomplete data, or intentional poisoning of the data, are other known dangers of the use of AI in medicine. Incomplete data sets may become harmful when applied to various minorities, such as ethnic, gender, or racial groups that have been excluded from the data.

STRATIFYHF is expected to improve HF health outcomes by facilitating early diagnosis, reducing the medical administrative burden, personalising medical outcomes, monitoring healthcare parameters on an individual basis, and allowing clinicians to spend more time with their patients.

STRATIFYHF will develop two Medical Innovations, the DSS and the Medical Mobile App with a potential to become certified medical devices, which will involve AI module(s), either as a stand-alone software or embedded into another device - system. The regulatory approach which will be used by the STRATIFYHF Consortium as a potential legal manufacturer(s) of these "products "will face barriers in the following key areas:

I. **Ethical:** Ensuring data privacy and security, preventing bias in algorithms, maintaining patient autonomy, and addressing potential conflicts of interest in research and development.
II. **Technological:** Data interoperability, data privacy, algorithmic bias, and explainability are the main challenges, along with issues related to technology adoption and usability.

III. **Liability:** Major concerns about the system's accuracy, potential for errors, and responsibility for patient outcomes raise questions about who would be liable if the STRATIFYHF DSS-based decision might lead to adverse patient outcomes.
IV. **Regulatory:** Initial concerns are related to Data interoperability, privacy concerns, technical limitations, and the need for robust validation and evidence-based design.
V. **Workforce:** A lack of adequate training for healthcare providers, limited teamwork and communication within healthcare teams, insufficient resources for health promotion, and uncertainties regarding clinical practice and guideline adherence.
VI. **Social:** Lack of social support, limited access to resources, and cultural and language barriers.
VII. **Clinical validation:** This process could be one of the most difficult since it involves gathering real-world patient data to assess the DSS's performance in predicting risk, diagnosing, and managing heart failure. The validation process aims to ensure the DSS is accurate, reliable, and useful for clinicians in making informed decisions.
VIII. **High implementation costs:** Hidden or not properly projected costs are potentially impacting their widespread adoption and effectiveness. These costs include both initial Design and Development bust also Verification and Validation Costs as well as ongoing operational and maintenance expenses.
IX. **Data quality and availability:** DSS and Medical Mobile Apps require both high-quality and accessible data. Data quality issues, such as missing values, errors, and inconsistencies, can lead to inaccurate DSS predictions, while insufficient data availability can limit the system's generalizability.
X. **Skilled workforce:** Such developmental efforts, like the ones by STRATIFYHF requires professionals with expertise in both medical and technical domains, including cardiologists, heart failure nurses, and other healthcare professionals with in-depth knowledge of HF diagnosis, treatment, and patient management. Additionally, the workforce needs data scientists, software engineers, and AI specialists with experience in building and implementing DSS for healthcare applications.
XI. **Patient safety barriers[102]:** Include unclear system responsibilities, threats to clinicians' autonomy, and excessive workload from alerts. Additionally, concerns about the impact on the doctor-patient relationship and potential data inaccuracies can also **pose** challenges.

In principle, defining and understanding the barriers preventing the acceptance and implementation of AI in the setting of healthcare will enable clinical staff and healthcare leaders to overcome the identified hurdles and incorporate AI technologies for the benefit of patients and clinical staff.

Barriers to AI in the health sector include data quality and availability, high implementation costs, lack of skilled workforce, regulatory and ethical concerns, and resistance to change from healthcare professionals. Additionally, ensuring interoperability with existing healthcare systems is a significant challenge.

9. References

The references to external documents (Regulations, International standards, etc.) have been introduced as footnotes, where necessary.

[102] de Vries AE, van der Wal MH, Nieuwenhuis MM, de Jong RM, van Dijk RB, Jaarsma T, Hillege HL, Jorna RJ. Perceived barriers of heart failure nurses and cardiologists in using clinical decision support systems in the treatment of heart failure patients. BMC Med Inform Decis Mak. 2013 Apr 26;13:54. doi: 10.1186/1472-6947-13-54. PMID: 23622342; PMCID: PMC3651365.