STUDY PROTOCOL

Official Title

Clinical Validation Study of Naevia Medical, a Clinical Decision Support System, in Heart Valve Disease

Brief Title

Validation of Naevia Medical in Valvulopathies

Date 03/03/2025

NCT Number NCT06392464

Unique Protocol Id 2024/104

Name of the Sponsor

Dilemma Solutions S.L.

Brief Summary

The study aims to validate naevia medical, a knowledge-based clinical decision support system (CDSS), for clinical benefit and safety in cases of cardiac valvulopathies. Using a series of retrospective clinical cases of heart valve disease, the research will evaluate the number of appropriate and inappropriate recommendations during baseline measurement (conventional management) and after CDSS activation.

00. CLINICAL EVALUATION PLAN

CEP

PRODUCT: "NAEVIA MEDICAL"

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	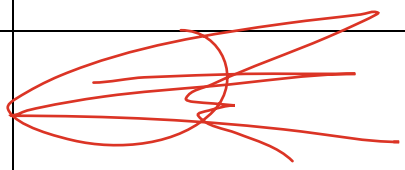	
2025/03/03	2025/03/03	2025/03/03

Reason for the last update
Ver. 1 – Fist Clinical Evaluation Plan according to the Regulation (EU) 2017/745 on medical devices.

TABLE OF CONTENTS

1. Purpose / Objective of Clinical Evaluation Plan

As required under Article 61 and Annex XIV, Part A (1)(a) of Regulation (EU) 2017/745 (hereafter MDR), this Clinical Evaluation Plan (CEP) is to establish, specify and justify critical aspects related to the device under evaluation (DUE) before proceeding with subsequent steps to locate, appraise and analyse available clinical data and prior to establishing the Clinical Evaluation Report (CER).

In particular this CEP provides the basis and justification for the level of clinical evidence required for the DUE.

The level of clinical evidence is determined in view of the characteristics of the device and its intended purpose and is fundamental to enable the acceptability of the benefit-risk ratio to be established.

Methods to enable identification and evaluation of available clinical data relevant to the DUE and its intended use are specified, in order to enable a conclusion to be reached concerning the sufficiency of the available clinical data establishing the safety and performance of the device.

2. Scope of the Clinical Evaluation Plan

This Clinical Evaluation Plan is related to the Clinical Evaluation of the following device (family):

NAEVIA MEDICAL

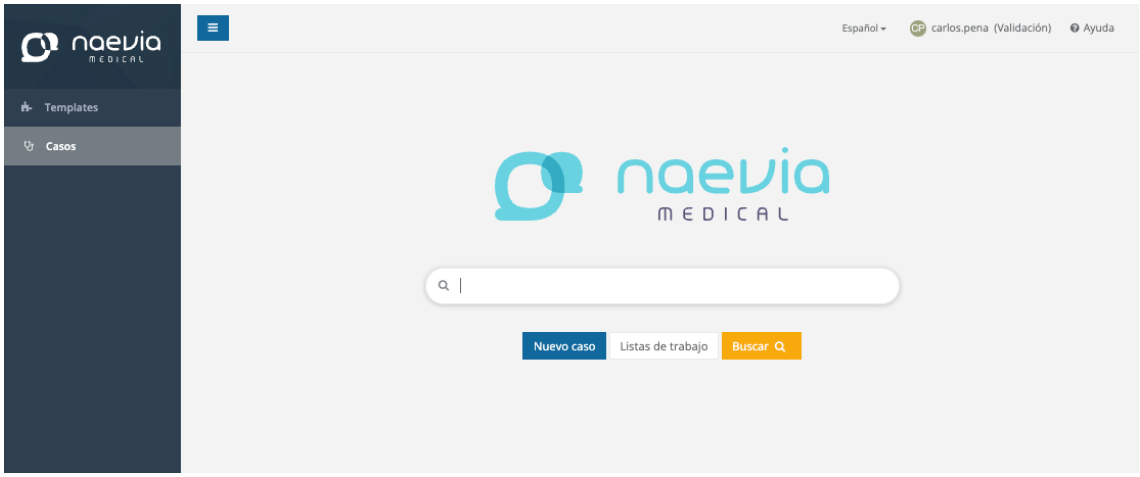

Figure 1. *NAEVIA MEDICAL picture*

REFERENCE	PRODUCT NAME / SHORT DESCRIPTION	UDI-DI (GTIN14)
NAEVIA MEDICAL	NAEVIA MEDICAL	(01)08437026776015

3. Product description

NAEVIA MEDICAL is software whose ultimate purpose is to provide support to physicians in the process of applying medical practice and scientific clinical knowledge. It is based on the clinical decision support systems (CDSS) paradigm.

Naevia Medical does not use artificial intelligence technologies such as machine learning or generative systems. Instead, it is based on an expert system composed of clinical rules made and validated by healthcare professionals, derived from reliable sources of knowledge and subjected to a rigorous peer-review process.

The solution is implemented on a robust .NET-based platform, fully leveraging the capabilities of the Visual Studio IDE to create an integrated, high-productivity development environment. The programming languages used during its development were C#, JavaScript, HTML and CSS, allowing the development of both back-end components and interactive and responsive user interfaces. This architecture promotes modularity and code reusability, facilitating the scalable and maintainable integration of new modules and functionalities. Furthermore, standardized coding practices and design patterns are adopted to enable early error detection through automated testing and static code analysis, ensuring quality and efficiency at every stage of the development lifecycle. Overall, this technical approach not only maximizes development efficiency but also guarantees the software’s adaptability and evolution in response to future technological demands.

The system is designed with a strong emphasis on compatibility, ensuring seamless integration with future upgrades, multiple Software of Unknown Provenance (SOUP) components, and various device versions. To achieve this, the architecture follows a modular and loosely coupled approach, allowing individual components to be updated or replaced without impacting overall system functionality. The implementation adheres to industry best practices to facilitate interoperability across different software versions and hardware platforms. Additionally, rigorous version control and continuous integration practices are employed to guarantee stability and reliability as the system evolves. This approach minimizes disruptions, enhances maintainability, and ensures long-term adaptability to technological advancements.

A fundamental aspect to maintain the security of critical areas in applications is to perform a correct validation of input and output data. In naevia's platform, exhaustive validations of input and output data are implemented and must be complemented by the relevant functional or business logic validations:

Validations are always performed on the server side. Client-side validations can also be useful, but are sufficient.

Fully cover data validation using validation schemes or standard mechanisms that ensure data entry by means of: sanitizations, data type, format, lengths, values, whitelists, blacklists, etc.

Ensure that structured data is strongly typed and validated according to a defined scheme, including allowed characters, length and pattern.

Verify that unstructured data is sanitized to impose generic security measures, such as allowed characters and length, and avoid potentially harmful characters.

Ensures that all untrusted input is properly sanitized using a sanitization library.
Avoid displaying sensitive information as a result of a validation error for any parameter received.
It accepts only the expected data at each application entry point that comes from the user, from the end process of all input fields, forms, URLs, application cookies, etc. Any unexpected data should be rejected

Verify that server-side input validation errors result in rejection of the request.

Ensures that all database queries are protected using parameterized queries to prevent SQL injection.
Checks that the application is not susceptible to command injection.
Checks that the application does not contain mass parameter assignment vulnerabilities (AKA automatic variable binding). Ensure that all input data is validated, not just HTML form fields, but all input sources such as REST requests, query parameters, HTTP headers, cookies, batch files, RSS feeds, etc., using whitelists, lesser forms of validation such as greylists (which remove known bad strings) or blacklists (which reject bad input).

The product is a Class IIa medical device according to Rule 11 of Annex VIII of the MDR.

It belongs to the following device categories:

GMDN CODE	GMDN TERM	DESCRIPTION
61087	Clinical management support software	An application software program intended to facilitate clinical management decisions by receiving structured patient data from electronic health records and/or manually-entered information (e.g., demographics, diagnostic/laboratory results) and returning clinical care information (e.g., reports, pedigree diagrams, reminders, post-therapy prognosis/risk score, anesthesia/pharmaceutical dosage, and/or links to guidelines) to a healthcare professional responsible for patient care; it is not primarily intended to analyse or manage diagnostic/patient images. Otherwise known as clinical decision support (CDS) software, it may be a locally installed program, web-based, or mobile application.

EMDN CODE	CATEGORY	CATEGORY DESCRIPTION	EMDN CODE DESCRIPTION
V92	V	Various devices	Medical device software - not included in other classes

3.1. Special characteristics of the device that may pose safety concerns

The DUE does not include medicinal, human, or animal components. It does not have any special characteristics that could pose new safety concerns.

4. General safety and performance requirements that require support from relevant clinical data

For the DUE, and following the Annex XIV (Part A, Section 1) of the MDR, the General Safety and Performance Requirements (GSPR) extracted from the Annex I that require support from relevant clinical data are:

[GSPR #1] Devices shall achieve the performance intended by their manufacturer and shall be designed and manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose. They shall be safe and effective and shall not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety, taking into account the generally acknowledged state of the art.

Relevant clinical data are to be located concerning:

- Device clinical performance. Increasing the number of appropriate diagnostic and therapeutic recommendations compared to conventional medical management.
- Device clinical safety. The product aims to provide this support safely for the patient, without generating inappropriate recommendations under normal conditions of use.
- Clinical conditions of the patient population and clinical outcomes following use of the device
- Clinical benefits related to the use of the device. Increasing adherence to scientific recommendations
- Clinical risks related to the use of the device. Generate recommendations and suggestions of knowledge that do not apply to the patient's data.
- Acceptability of the benefit-risk profile → Compatibility with a high level of protection of health and safety

The purpose of the product is to add value to healthcare professionals in the decision-making process by increasing appropriate recommendations based on scientific evidence and decreasing inappropriate recommendations. Its use aims to promote the practice of scientific medicine, with greater adherence to scientific recommendations that have been shown to improve patient outcomes.

It is important to emphasize that naevia medical does NOT replace the physician nor does it make autonomous decisions regarding patient management; its function is limited to presenting a prioritized series of knowledge recommendations that the professional can review and choose to adopt or not. These recommendations are explainable by showing the facts that triggered the recommendation, reproducible, and supported by information referenced in bibliographic citations. In this regard, naevia medical does NOT use artificial intelligence algorithms based on case learning nor does it employ generative technologies.

The product aims to provide this support safely for the patient, without undesirable side effects or adverse events under normal conditions of use.

[GSPR #2] The requirement in [Annex I of the MDR] to reduce risks as far as possible means the reduction of risks as far as possible without adversely affecting the benefit-risk ratio.

Relevant clinical data are to be located concerning:

- Acceptability of the benefit-risk profile → Compatibility with a high level of protection of health and safety

The risk-benefit relationship is favourably justified when the benefits in improving the quality of care, increasing appropriate recommendations, and decreasing inappropriate ones outweigh the risks associated with the use of CDSS. This requires careful modelling of knowledge, correct implementation, constant monitoring, and continuous updating. Acceptance of the system by clinical users is crucial and must be ensured through appropriate training, support, and participation in system improvement.

Deterministic rules are widely used for problem-solving. The application of a set of clinical rules to the specific data of a patient enables the logical generation of recommendations and allows for the review of knowledge that applies to a particular case. However, it should be considered that there is intrinsic uncertainty in each decision-making problem, and the medical knowledge managed by a system has limitations.

With the objective of reducing risks the knowledge modelling and rule-making system of naevia medical facilitates semantically well-formed rules with coherent logic. The peer review process aims to ensure that the variables and propositions used have the same meaning as the texts of the recommendations they intend to model.

[GSPR #4] Risk control measures adopted by manufacturers for the design and manufacture of the devices shall conform to safety principles, taking account of the generally acknowledged

state of the art. To reduce risks, Manufacturers shall manage risks so that the residual risk associated with each hazard as well as the overall residual risk is judged acceptable. In selecting the most appropriate solutions, manufacturers shall, in the following order of priority: ***(a)*** *eliminate or reduce risks as far as possible through safe design and manufacture;* ***(b)*** *where appropriate, take adequate protection measures, including alarms if necessary, in relation to risks that cannot be eliminated; and* ***(c)*** *provide information for safety (warnings/precautions/contra-indications) and, where appropriate, training to users. Manufacturers shall inform users of any residual risks.*

Relevant clinical data is to be located concerning:

- Generally acknowledged state of the art as related to clinical, biological, and technical aspects of the DUE
- Information for safety / training to users currently provided with similar devices on the market
- Known and foreseeable residual risks currently related to similar devices on the market

[GSPR #5] In eliminating or reducing risks related to use error, the manufacturer shall ***(a)*** *reduce as far as possible the risks related to the ergonomic features of the device and the environment in which the device is intended to be used (designed for patient safety), and* ***(b)*** *give consideration to the technical knowledge, experience, education, training and use environment, where applicable, and the medical and physical conditions of intended users (design for lay, professional, disabled or other users).*

Relevant clinical data is to be located concerning:

- Specific usability / use-error risks that are known or foreseeable
- Information for safety / training to users currently provided with similar devices on the market

Naevia medical is designed to be used by physicians after a short training period aimed at eliminating any errors in usage. Specific usability/use-error risks that are known or foreseeable should be considered. Safety/training information currently provided to users of similar devices on the market must also be taken into account. The transparency of the software's knowledge recommendations, which simply explain the conditions that triggered them, allows the professional to interact with and critically analyze the suggestions.

[GSPR #6] The characteristics and performance of a device shall not be adversely affected to such a degree that the health or safety of the patient or the user and, where applicable, of other persons are compromised during the lifetime of the device, as indicated by the manufacturer, when the device is subjected to the stresses which can occur during normal conditions of use and has been properly maintained in accordance with the manufacturer's instructions.

Relevant clinical data is to be located concerning:

- Normal conditions of use of the DUE, including other devices interconnected or used together with the DUE
- Information for proper maintenance currently provided with similar devices on the market
- Clinical data to support the clinical safety and performance of the device throughout the claimed lifetime of the device.

The system's knowledge is updated throughout the lifetime of the knowledge version, incorporating the necessary fine-tuning to facilitate updating and the correct interpretation of the recommendations. This includes normal conditions of use and clinical data to support the clinical safety and performance of the device throughout its claimed lifetime.

[GSPR #8] All known and foreseeable risks, and any undesirable side-effects, shall be minimised and be acceptable when weighed against the evaluated benefits to the patient and/or user arising from the achieved performance of the device during normal conditions of use.

Relevant clinical data are to be located concerning:

- State of the art concerning known clinical risks and side-effects
- Clinical benefits related to the use of the device
- Clinical risks related to the use of the device
- Acceptability of the benefit-risk profile

Risks and potential adverse effects will be monitored and controlled.

In relation to the potential benefits, Naevia medical provides recommendations to doctors based on the latest evidence and clinical guidelines, supporting informed and updated decision-making. It promotes consistency in care by standardizing data presentation and encouraging evidence-based practice, reducing variability in patient treatment and clinical inertia. Additionally, the CDSS reduces medical errors by offering knowledge-based suggestions, particularly in high-pressure environments with complex patients, and serves as an educational tool, keeping professionals informed about scientific updates while they perform their clinical duties.

*[GSPR #23] Label and instructions for use: **(4)** Information in the instructions for use **(e)** the performance characteristics of the device.*

Relevant clinical data are to be located concerning:

- State of the art concerning known clinical risks

Detailed usage instructions on the platform itself, as well as updated information on the latest evidence.

5. Specification of the intended purpose of the device

Naevia Medical is a clinical decision support software (CDSS) that, based on clinical input data (history, symptoms, complementary test data...) of adult patients with heart disease, provides healthcare professionals with prioritized, justified and referenced recommendations and knowledge suggestions related to diagnosis and/or treatment (recommended tests, medications, interventions,..).

6. Intended target groups and user, indications, and contraindications

Intended target groups

- Adult patients with valvular heart disease, offering diagnostic, prognostic and therapeutic recommendations.

Intended users

Medical doctors or residents who are familiar with the user manual and how to use the tool.

Indications

- Naevia medical is indicated, as part of the assessment of a patient by healthcare professionals, to assist in making diagnostic prognostic and therapeutic decisions of patients suffering from valvular heart disease.

Contraindications

Population under 18 years of age.

Medical emergency situations.

7. Description of intended clinical benefits to patients. Clinical outcome parameters.

It is expected that, compared to conventional clinical management without a clinical decision support system, naevia will increase the number of appropriate recommendations and significantly reduce the number of inappropriate and absent recommendations in all the domains analyzed.

7.1 Direct clinical benefit to provide healthcare professionals with recommendations and suggestions for knowledge related to diagnosis, prognosis and/or treatment

- Positive impact on enhancing the ability of healthcare professionals to provide a greater number of recommendations appropriate to each patient's specific situation, supporting diagnostic and clinical decision making.

Naevia medical provides recommendations based on the latest evidence and clinical guidelines, supporting informed and updated decision-making. It promotes consistency in care by standardizing data presentation and encouraging evidence-based practice, reducing variability in patient treatment and clinical inertia. Additionally, the CDSS reduces medical errors by offering knowledge-based suggestions, particularly in high-pressure environments with complex patients, and serves as an educational tool, keeping professionals informed about scientific updates while they perform their clinical duties.

Naevia Medical has developed an advanced platform for managing clinical data, which has demonstrated its effectiveness, acceptability and usability in various studies. This platform has been key in COVID-19 research, especially in cardiac diseases such as cardiomyopathies and heart failure.

<u>Evidence from pre-clinical evaluation</u>

- Through the system functions and features, users have to be able to get recommendations and suggestions for knowledge related to diagnosis, prognosis and/or treatment.
    - V&V per EN ISO 62304 and install validation. All tests provide recommendations and suggestions and thus CDSS is verified by all tests.
    - V&V per EN 82304 and install validation. All tests provide recommendations and suggestions and thus CDSS is verified by all tests.
    - Usability testing of the software by representative users to successfully provides recommendations and suggestions for knowledge related to diagnosis, prognosis and/or treatment.

- Capability of Naevia medical in the management of patients with cardiovascular diseases: a pre-clinical study of simulated cases in patients with valvular heart disease, using the “2021 ESC/EACTS Guidelines for the management of valvular heart disease”, must validate the Naevia medical’s capability in the management of patients with valvular heart disease.

<u>Evidence from clinical evaluation/investigations</u>

- Software enables to provide recommendations and suggestions for knowledge related to diagnosis, prognosis and/or treatment: scientific literature confirms that SW system functions and features are aligned with current user requirements as described in relevant publications and as included in the DUE.

- Increase of appropriate recommendations: number of appropriate recommendations – an observational, single-centre study consisting on a clinical validation of a CDSS applied to retrospective clinical cases of cardiology patients with valvular heart disease, shall confirm an increase in the number of appropriate recommendations by by a factor of three over the recommendations generated with general management without the support system.

- Inappropriate recommendations: number of inappropriate recommendations – an observational, single-centre study consisting on a clinical validation of a CDSS applied to retrospective clinical cases of cardiology patients with valvular heart disease, shall confirm that naevia medical, compared to conventional management, is able to reduce the number of inappropriate and mising recommendations based on scientific evidence in the diagnostic and therapeutic areas.

- Concordance between expert evaluators:

    - The analysis of the degree of agreement/disagreement in the different domains, evaluated using a Likert scale, analysed using ordinal regression (Joshi, Kale et al. 2015). Response options: 1. Strongly disagree, 2. Disagree, 3. Neither agree nor disagree, 4. Agree, 5. Strongly agree.
    - The panel's agreement with the CDSS was very high, with a mean Likert scale score above 4 in all domains (STD: 4.53, LTD: 4.68, CMT: 4.58, ITI: 4.62). The probability of strongly agreeing was significantly higher than the probability any of the other categories (z.ratio (5|1)= 30.88, p-value< 0.001, z.ratio (5|2)= 31.67, p-value < 0.001, z.ratio (5|3) = 30.21, p-value< 0.001, z.ratio (5|4)= 22.54, p-value< 0.001).

<u>Evidence from registries</u>

Additionally, Naevia Medical's platform has been or is being used in other significant registries, such as:

- The "REDMIO20: Spanish Registry of Dilated Cardiomyopathy due to RBM20 Gene Mutation," a multicenter registry coordinated by Dr. Eduardo Villacorta from the Salamanca University Assistance Complex, which included 168 cases up to December 11, 2023.
- The "PROCeso asistencial integrado de Estenosis Aórtica grave Sintomática (PROCEAS)" 2020/405 registry, led by Dr. Violeta González-Salvado from the Santiago de Compostela University Clinical Hospital, with 991 cases of aortic stenosis registered up to December 11, 2023.

Evidence from post-market surveillance:

- PMS evidence to evaluate the absence of complications and low incidence of adverse events.
- Recommendations that could lead to a serious adverse event shall be identified as patient safety risks, including:
    - Possibility of death.
    - The need for a medical or surgical intervention that would not otherwise be necessary.
    - Omission of critical recommendations that could adversely affect the patient's prognosis.

8. Alternative options for treatment, diagnostic and/or management

The alternative to CDSS is conventional clinical management, where doctors alone face complex patients with limited decision time, contributing to medical errors (Newman-Toker, Nassery et al. 2023) (Makary and Daniel 2016). CDSS can reduce errors caused by oversight (Avery, Sheehan et al. 2021), but medical decisions still depend on doctors' experience, leading to avoidable harm and costs (Makary and Daniel 2016, 2017, Avery, Sheehan et al. 2021) (Bates and Gawande 2003, Shrank, Rogstad and Parekh 2019).

Many patients do not receive the benefits of scientific medical recommendations (Ghazi, Yamamoto et al. 2022, Bhatt, Varshney et al. 2023), despite the increase in health record data and new clinical guidelines (Balas and Boren 2000, Obermeyer and Lee 2017). Limited consultation time, patient complexity, and provider inexperience increase care variability (Singh and Sittig 2015, Jarjour, Henri et al. 2020).

Medical progress relies on doctors' decisions and patient adherence (Walewska-Zielecka, Religioni et al. 2021, Fonarow, Yancy et al. 2011). However, doctors often use heuristics—mental shortcuts that speed decisions but cause cognitive biases (Blumenthal-Barby and Krieger 2015). These biases, influenced by past experiences, clinical inertia, and patient factors like age or sex, affect decision accuracy (Blumenthal-Barby and Krieger 2015).

9. Clinical Evaluation Strategy – Relevant clinical data and information about the state of the art – Sources and strategies to locate data. Methods to be used to assess data.

9.1 Outline of the clinical evaluation strategy following Article 61 MDR

Naevia medical is a Class IIa medical device software.

Following Article 61(3) of the MDR, the clinical evaluation is based on:

(a) A critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics and intended purpose of the device, meeting the following conditions as described in the clinical evaluation report:

- It is demonstrated that this generation of Naevia medical subject to clinical evaluation for the intended purpose is potentially equivalent to the device to which the data relate, in accordance with Section 3 of Annex XIV, and
- It is shown that the data adequately demonstrate compliance with the relevant GSPRs.

(b) A critical evaluation of the results of all available clinical investigations, taking duly into consideration whether the investigations were performed under Articles 62 to 80 MDR, and acts adopted pursuant to Article 81 MDR, and Annex XV, and

(c) A consideration of the currently available alternative treatment options for the same intended purpose.

Moreover, Article 61(4) of the MDR, in the case of implantable devices and class III devices, clinical investigations shall be performed, except if:

— the device has been designed by modifications of a device already marketed by the same manufacturer,
— the modified device has been demonstrated by the manufacturer to be equivalent to the marketed device, in accordance with Section 3 of Annex XIV and this demonstration has been endorsed by the notified body, and
— the clinical evaluation of the marketed device is sufficient to demonstrate conformity of the modified device with the relevant safety and performance requirements.

This consideration enables a clinical evaluation strategy with the requirement to not perform specific pre-market clinical investigations with the DUE with the condition that clinical data provided from the equivalent device is sufficient and clinical evidence is available.

Per Article 2(48) MDR, ‘clinical data’ means:

Any information concerning the safety or performance that is generated from the use of a device and is sourced from the following:

— Clinical investigation(s) of the device concerned,
— Clinical investigation(s) or other studies reported in scientific literature, of a device for which equivalence to the device in question can be demonstrated,
— Reports published in peer reviewed scientific literature on other clinical experience of either the device in question or a device for which equivalence to the device in question can be demonstrated,
— Clinically relevant information coming from post-market surveillance, in particular the post-market clinical follow-up.

Clinical data are sourced from clinical investigations of the DUE to support its specific clinical performance aspects.

In addition, despite meeting the regulatory definition of 'clinical data' through undergoing a clinical investigation with the device concerned, other sources of relevant information are considered, specifically pre-clinical data related to the DUE itself together with data pertaining to similar devices, to establish the current state of the art along with the criteria for the assessment of the safety and performance of this type of device. Data concerning similar devices and current alternatives are considered as supporting data and to enable planning of PMS and PMCF activities.

The scientific quality of the available datasets is assessed during the appraisal stage of the clinical evaluation. Appraised datasets that qualify as 'clinical data' (as defined in Article 2 (48) of the MDR) are included in the analysis to determine if the available information provides sufficient clinical evidence.

9.2 Sources and strategy to collect data

Based on current experience during product development as well as information known to be available regarding other similar products, the following strategies are to be used to locate and gather all relevant information:

(i) Initial general searches to establish the parameters used to determine the acceptability of the DUE benefit-risk ratio, and to identify early clinically relevant information pertinent to the DUE and its intended use. Preliminary general searches also contribute to elaborate an accurate PICO strategy for the literature review, and to establish more specific search terms with the purpose of obtaining state-of-the-art relevant data.

(ii) Searches of peer-reviewed scientific literature to establish the scientific basis, technical and clinical requirements as related to the identified clinical need, clinical conditions, standard of care, state of the art, similar devices, and alternative treatment methods.

(iii) Search and review of background and clinical experience as related to similar devices, including clinically relevant information coming from post-market surveillance and/or post-market clinical follow-up.

(iv) Search of scientific literature with published results of clinical investigation(s) and other studies to determine:
   a. Possible benefits
   b. Possible risks, side-effects and harm that may have been due to the DUE or similar devices
   c. Safety information as related to the DUE or similar devices.

(v) (In-house / Unpublished) Clinical investigation report(s) as related to the device concerned.

Strategy (i) will be used to define the clinical evaluation scope, the regulatory strategy, and the framework for the design of the consequent literature searches. These preliminary State of the Art Results should drive the Safety and Performance objectives for the DUE.

Strategies (ii) and (iii) will be used to establish the clinical aspects and characteristics for which ample scientific, technical and/or clinical data are believed to be already available.

Strategy (iv) will be used to locate clinically relevant data sets for the device concerned or for reference devices that may be demonstrated to be equivalent.

Strategy (v) will be used if the device itself has undergone clinical investigation, clinical trial, or other clinical study.

The following sources shall be considered:

- Scientific databases: PubMed
- Systematic review databases: Cochrane library
- Manual searches (internet searches, vigilance databases, non-published data and Citations referenced in scientific literature).

The clinical evaluation for the device under evaluation is planned, conducted, and documented according to article 61 and Annex XIV part A of the MDR and applicable MDCG guidelines. Nevertheless, the MEDDEV 2.7/1 (Rev.4 of June 2016) is useful to structure the clinical evaluation, to establish an appraisal plan and to establish the different stages of the Clinical Evaluation process (see figure 2 below).

Stage 0: Clinical Evaluation Scoping and Planning (as set out in this document)

Stage 1: Identification of clinical data relevant to the device and its intended use (as described above), and any gaps in clinical evidence, through a systematic scientific literature review. The details of the literature review to be conducted are established in a Literature Search Protocol. This protocol defines the specific search terms and search algorithms to be applied (as determined by current knowledge of the device, the conditions of use, intended use, indications for use), inclusion and exclusion criteria to be applied to articles and data sets found and to determine which datasets can only be considered as contribution to information about the state of the art and which datasets meet the definition of “clinical data” and hence can be routed to the appraisal stage. If data pertaining to a similar device is considered, clinical, biological, and technical equivalence to the device under evaluation must first be demonstrated with sufficient explanation and rationale for any gaps found. Search terms and search algorithms are defined so that the search is repeatable, thorough, objective, and comprehensive (depth and extent are proportionate and appropriate to the nature classification, intended purpose and risks of the device) taking into account both favourable and unfavourable data.

Stage 2: Appraisal of all clinical data by evaluating their suitability for establishing the safety and performance of the device. The Literature Search Protocol also contains the appraisal plan and methods to be applied to assess all relevant clinical data by evaluating their suitability to establish the safety and performance of the DUE. The results of the execution of the Literature Search Protocol shall be documented in the Literature Search Report. A summary with the most relevant results and conclusions shall be extracted to the Clinical Evaluation Report.

Stage 3: Analysis of all relevant "clinical data" in order to reach conclusions about the safety and performance of the device, including its clinical benefits.

Appraised clinical data is analysed to determine if there is "sufficient clinical evidence" to conclude that the device is safe and achieves its intended benefits. The level of clinical evidence to be attained is specified in Section 13 below. The analysis contemplates relevant information collected concerning clinical benefits that are confirmed, quantification of risk frequency and severity as well as confirmation of the effectiveness of risk control measures, a qualitative and, if possible, quantitative determination of the benefit-risk ratio (e.g., marginally positive versus clearly positive) Any missing data or gaps in clinical data are identified. If it cannot be concluded that sufficient clinical evidence is available, then additional clinical data must be generated, e.g. through additional literature searching and/or through specific clinical investigations in accordance with the clinical development plan to address outstanding gaps and/or issues.

Stage 4: Clinical Evaluation Report. PMS Plan. PMCF Plan.

Results of the previous steps along with the conclusions concerning the availability of sufficient clinical evidence are documented, reviewed, and approved in the Clinical Evaluation Report. Ongoing steps to continuously update the clinical evaluation are set out in the PMS Plan and PMCF Plan.

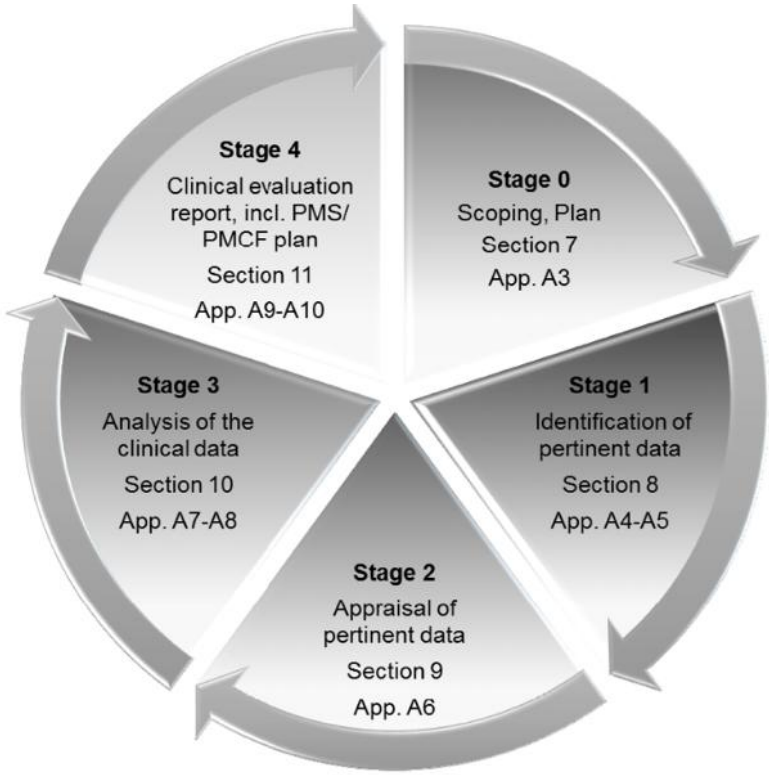

Figure 2. *Stages of Clinical evaluation according to MEDDEV 2.7/1 (Rev.4)*

9.3 Preliminary systematic review

A pilot scientific literature review was performed to identify initial State of the Art clinical data relevant to the device safety and performance objectives and its intended use, as detailed below.

Based on the results and outcomes from this preliminary search, the full PICO strategy, search terms and search algorithms are established and detailed in the Literature Search Protocol.

- **Search details:** "clinical decision support systems"[Title] NOT artificial intelligence / *Filters*: Review [*article type*], Systematic Review [*article type*], Humans [*species*] → 135 results

Search query: ("clinical decision support system"[Title]) AND ((y_5[Filter]) AND (humans[Filter]))

- **Search details:** "clinical decision support systems"[Title] NOT artificial intelligence AND recommendations / *No filters applied* → 84 results

Search query: ("clinical decision support systems"[Title] NOT ("artificial intelligence"[MeSH Terms] OR ("artificial"[All Fields] AND "intelligence"[All Fields]) OR "artificial intelligence"[All Fields])) AND ("recommend"[All Fields] OR "recommendable"[All Fields] OR "recommendation"[All Fields] OR

"recommendation s"[All Fields] OR "recommendations"[All Fields] OR "recommended"[All Fields] OR "recommending"[All Fields] OR "recommends"[All Fields])

- **Search details:** "ischemic heart disease"[Title] / *Filters*: in the last 5 years [*publication date*], Review [*article type*], Systematic Review [*article type*], Humans [*species*] → 142 results

Search query: ("ischemic heart disease"[Title]) AND ((y_5[Filter]) AND (review[Filter] OR systematicreview[Filter]) AND (humans[Filter]))

- **Search details:** "valvular heart disease"[Title] / *Filters*: in the last 5 years [*publication date*], Review [*article type*], Systematic Review [*article type*], Humans [*species*] → 91 results

Search query: ("valvular heart disease"[Title]) AND ((y_5[Filter]) AND (review[Filter] OR systematicreview[Filter]) AND (humans[Filter]))

- **Search details:** "clinical decision support system"[Title] AND (side effects OR adverse effects OR clinical risks) / *No filters applied* → 217 results

Search query: "clinical decision support system"[Title] AND ("adverse effects"[MeSH Subheading] OR ("adverse"[All Fields] AND "effects"[All Fields]) OR "adverse effects"[All Fields] OR ("side"[All Fields] AND "effects"[All Fields]) OR "side effects"[All Fields] OR ("adverse effects"[MeSH Subheading] OR ("adverse"[All Fields] AND "effects"[All Fields]) OR "adverse effects"[All Fields]) OR (("ambulatory care facilities"[MeSH Terms] OR ("ambulatory"[All Fields] AND "care"[All Fields] AND "facilities"[All Fields]) OR "ambulatory care facilities"[All Fields] OR "clinic"[All Fields] OR "clinic s"[All Fields] OR "clinical"[All Fields] OR "clinically"[All Fields] OR "clinicals"[All Fields] OR "clinics"[All Fields]) AND ("risk"[MeSH Terms] OR "risk"[All Fields] OR "risks"[All Fields])))

The following articles were considered relevant to reach the objective of this search. Another approach used to identify relevant information for the clinical evaluation of the DUE was the manual search used as a supplemental path to find the following additional relevant articles. Copies of the selected articles are gathered attached to the present document.

1. Muhiyaddin, R., Abd-Alrazaq, A. A., Househ, M., Alam, T., & Shah, Z. (2020). The Impact of Clinical Decision Support Systems (CDSS) on Physicians: A Scoping Review. Studies in health technology and informatics, 272, 470–473. https://doi.org/10.3233/SHTI200597
2. Sutton, R. T., Pincock, D., Baumgart, D. C., Sadowski, D. C., Fedorak, R. N., & Kroeker, K. I. (2020). An overview of clinical decision support systems: benefits, risks, and strategies for success. NPJ digital medicine, 3, 17. https://doi.org/10.1038/s41746-020-0221-y
3. Kwan, J. L., Lo, L., Ferguson, J., Goldberg, H., Diaz-Martinez, J. P., Tomlinson, G., Grimshaw, J. M., & Shojania, K. G. (2020). Computerised clinical decision support systems and absolute improvements in care: meta-analysis of controlled clinical trials. BMJ (Clinical research ed.), 370, m3216. https://doi.org/10.1136/bmj.m3216

4. Jensen, R. V., Hjortbak, M. V., & Bøtker, H. E. (2020). Ischemic Heart Disease: An Update. Seminars in nuclear medicine, 50(3), 195–207. https://doi.org/10.1053/j.semnuclmed.2020.02.007
5. Writing Committee Members, Otto, C. M., Nishimura, R. A., Bonow, R. O., Carabello, B. A., Erwin, J. P., 3rd, Gentile, F., Jneid, H., Krieger, E. V., Mack, M., McLeod, C., O'Gara, P. T., Rigolin, V. H., Sundt, T. M., 3rd, Thompson, A., Toly, C., ACC/AHA Joint Committee Members, O'Gara, P. T., Beckman, J. A., Levine, G. N., … Woo, Y. J. (2021). 2020 ACC/AHA guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *The Journal of thoracic and cardiovascular surgery*, *162*(2), e183–e353. https://doi.org/10.1016/j.jtcvs.2021.04.002
6. Graham, T. A., Kushniruk, A. W., Bullard, M. J., Holroyd, B. R., Meurer, D. P., & Rowe, B. H. (2008). How usability of a web-based clinical decision support system has the potential to contribute to adverse medical events. AMIA ... Annual Symposium proceedings. AMIA Symposium, 2008, 257–261.

10. Methods for assessment of clinical safety

Clinical safety concerns, including known residual risks and side-effects of medical device software, shall be identified from Risk analysis/Risk assessment, vigilance/adverse events databases and published scientific literature. Specific benefit-risk assessment includes the parameters described in Section 11 of the present report.

Identification of initial data concerned to clinical safety shall be identified through consultation of vigilance and/or adverse-events databases for similar devices. This strategy is also described in section 9 of the present document.

Specific databases that shall be used for clinical safety data identification are:

- Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) – Medical Devices Alerts
- Medicine and Healthcare Products and Regulatory Agency (MHRA) – Alerts and recalls for drugs and medical devices
- FDA Medical Devices Recalls
- FDA Total Product Life Cycle (TPLC)
- FDA Manufacturer and User Facility Device Experience (MAUDE)

The following sections detail the potential specific residual clinical risks and the foreseeable side effects related to the use of the device under evaluation that shall be addressed in the Clinical Evaluation and supported with clinical data.

As stated previously, the device has no special characteristic or novel features. However, residual risks will be addressed in the device risk management documentation to manage any special performance or safety concerns.

Clinical safety of the DUE will be determined:

- Indirectly on the basis of software verification and validation.
- Through the assessment of the characteristics of the finished device and fulfilment of technical specifications.
- Through review and assessment of clinical data assessing the safety and performance of similar / equivalent devices.
- Through review and assessment of incidents, adverse events, or other relevant safety reports for similar / equivalent devices.

In particular, information concerning potential specific residual clinical risks and the foreseeable side effects related to the use of the device under evaluation that shall be addressed in the Clinical Evaluation and supported with clinical data are gathered in the following sub-sections.

10.1. Residual risks

Residual risks were analysed and addressed following the Risk Management Plan. Risks that are relevant during clinical use and residual risks are listed below and shall be considered when searching for relevant clinical data.

Relevant risks during clinical use and residual risks are listed below and shall be considered when searching for pertinent clinical data to the DUE.

Risk ID	Risk	Description
2	Misdiagnosis caused by product's error	The user makes a clinical decision based on wrong recommendations.
3	Misdiagnosis caused by user's errors	The output data given by the software is not adequate for the patient. The user makes a clinical decision based on wrong recommendations.
4	Patient's privacy and data security	The output data given by the software is not adequate for the patient due to the corruption of patient's data. The user makes a clinical decision based on wrong recommendations.

10.2. Foreseeable side-effects

No side-effects have been identified for this device.

11. Basis to determine the acceptability of the benefit-risk ratio

Naevia Medical is a clinical decision support software (CDSS) that, based on clinical input data (history, symptoms, complementary test data...) of adult patients with heart disease, provides healthcare professionals with prioritized, justified and referenced recommendations and knowledge suggestions related to diagnosis and/or treatment (recommended tests, medications,...).

The main clinical benefit obtained with the DUE is the following:

- Direct clinical benefit to provide healthcare professionals with recommendations and suggestions for knowledge related to diagnosis, prognosis and/or treatment.

The main complications associated with the use of product category are the following:

- Misdiagnosis caused by product's error.
- Misdiagnosis caused by user's errors.
- Patient's privacy and data security.

The risk-benefit ratio is favorably justified when the benefits in improved quality of care, increased appropriate recommendations and decreased inappropriate recommendations outweigh the risks associated with the use of CDSS. This requires careful knowledge modelling, correct implementation, constant monitoring and continuous updating. Acceptance of the system by clinical users is crucial and must be ensured through appropriate training, support and participation in system improvement.

Clinical benefits and possible complications or side effects related to the use of naevia Medical will be further investigated and assessed in the planned literature searches and included in the Clinical Evaluation Report (see Benefit-Risk Analysis in section 5 of the Technical Documentation).

Based on the state of the art in medicine, the acceptability of the DUE benefit-risk ratio for the indications mentioned above, depends on clinical safety and performance parameters and outcomes as listed below.

***Table 1** – Naevia Medical – Indicative List of Clinical Safety and Performance Parameters and Quantitative Measures*

Parameter / Outcome	Quantitative Measure of Performance	Source / Level of Evidence Required	
Performance of Naevia medical to provide healthcare professionals with recommendations and suggestions for knowledge related to diagnosis, prognosis and/or treatment			
Software enables to provide recommendations and suggestions for knowledge related to diagnosis, prognosis and/or treatment	Goal: all basic key characteristics of CDSS are supported and all supported characteristics work correctly and as expected. [references to sources] *EN ISO 62304 – Medical device software – Software life-cycle processes EN 82304 – Health Software – Part 1: General requirements for product Safety	Preclinical	Accepted if using the system functions and features, users are able to get recommendations and suggestions for knowledge related to diagnosis, prognosis and/or treatment. - V&V per EN ISO 62304 and install validation. All tests provide recommendations and suggestions and thus CDSS is verified by all tests. - V&V per EN 82304 and install validation. All tests provide recommendations and suggestions and thus CDSS is verified by all tests. - Usability testing of the software by representative users to successfully provides recommendations and suggestions for knowledge related to diagnosis, prognosis and/or treatment.
		Clinical	Accepted if system features cover user needs for getting recommendations and suggestions for knowledge related to diagnosis, prognosis and/or treatment aligned with the tools required for medical diagnosis support and using the system functions and features, users successfully use CDSS to make clinical decisions regarding diagnosis, prognosis and/or treatment. - V&V per EN ISO 62304 and install validation. All tests provide recommendations and suggestions and thus CDSS is verified by all tests*. - V&V per EN 82304 and install validation. All tests provide recommendations and suggestions and thus CDSS is verified by all tests.

			- Usability testing of the software by representative users to successfully provide recommendations and suggestions for knowledge related to diagnosis, prognosis and/or treatment.
Capability of Naevia medical in the management of patients with cardiovascular diseases	Goal: Naevia medical is capable to manage patients with cardiovascular diseases [reference to sources] *Lorenzo Monserrat, Roberto Barriales-Villa, Fernando De Frutos, José María Larrañaga, Ángela López Sainz, Carlos Peña Gil, Belén Peiró, Nerea Mora, Lorena Gómez-Burgueño, Marta Fernández-Galindo, Rocío Blanco, Victoria Espejo, Iago Mosquera, Lidia María Carrillo, Francisco José Bermúdez, David López-Cuenca, Blanca Figueres, Alicia Ferradas, Javier Pumares, Carmen Zapata, Eduardo Villacorta, Nicolas López-Canoa, Eva Cabrera, María Isabel García-Álvarez, Elías Grande, Javier Loureiro, Eloy Sobrido, Óscar Vázquez, Valentina Capelli, Enrique Jiménez-Jáimez, Juan Jiménez-Jaímez, Pablo García-Pavía, Tomás Ripoll-Vera, Vicente Climent-Paya, Julián Palomino-Doza, y Juan Ramón Gimeno-Blanes. Development and pre-clinical evaluation of an advanced decision support system for hypertrophic cardiomyopathy clinical management Vahanian, A., Beyersdorf, F., Praz, F., Milojevic, M., Baldus, S., Bauersachs, J., Capodanno, D., Conradi, L., De Bonis, M., De Paulis, R., Delgado, V., Freemantle, N., Gilard, M., Haugaa, K. H., Jeppsson, A., Jüni, P., Piérard, L., Prendergast, B., Sádaba, J. R., . . . Sharipov, I. (2021). 2021 ESC/EACTS Guidelines for the management of valvular heart disease. European Heart Journal,	Preclinical	- A pre-clinical study of simulated cases in patients with valvular heart disease, using the "2021 ESC/EACTS Guidelines for the management of valvular heart disease", must validate the Naevia medical's capability in the management of patients with valvular heart disease*.
		Clinical	- Clinical studies and registries must show that Naevia medical is capable to manage patients with cardiovascular diseases by providing healthcare professionals with recommendations and suggestions for knowledge related to diagnosis, prognosis and/or treatment.

	43(7), 561-632. https://doi.org/10.1093/eurheartj/ehab395		
Appropriate recommendations	Increase the number of appropriate recommendations by a factor of three	Clinical	- An observational study consisting on a clinical validation of a CDSS applied to retrospective clinical cases of cardiac patients with valvular heart disease, shall confirm an increase in the number of appropriate recommendations by a factor of three over the recommendations generated with conventional management without the support system.
Inappropriate recommendations	Reduction of inappropriate recommendations	Clinical	- An observational study consisting on a clinical validation of a CDSS applied to retrospective clinical cases of cardiac patients with valvular heart disease, shall confirm that Naevia medical, compared to conventional management, is able to significantly decreased the number of inappropriate and missing recommendations in all the domains analyzed.

Concordance between expert evaluators	Professionals agreement [reference to sources] *Joshi, A., S. Kale, S. Chandel and D. K. Pal (2015). "Likert Scale: Explored and Explained." Current Journal of Applied Science and Technology 7: 396-403.	Clinical	- The panel's agreement with the CDSS was very high, with a mean Likert scale score above 4 in all domains (STD: 4.53, LTD: 4.68, CMT: 4.58, ITI: 4.62). The probability of strongly agreeing was significantly higher than the probability any of the other categories (z.ratio (5|1)= 30.88, p-value< 0.001, z.ratio (5|2)= 31.67, p-value < 0.001, z.ratio (5|3) = 30.21, p-value< 0.001, z.ratio (5|4)= 22.54, p-value< 0.001). -
Safety of Naevia medical			
Misdiagnosis caused by product's error	Incidence with SW System not > documented incidence with similar devices	Clinical	- Incidents and adverse events (if any) related to the DUE and linked to misdiagnosis caused by product's error in the DUE do not result in serious harm, injury or impairment to the patient. o No serious clinical complications or other effects linked to misdiagnosis caused by product's error in the DUE are observed in the clinical studies and registries performed with the DUE.
			- Incidents and adverse events (if any) related to the DUE and linked to misdiagnosis caused by product's error in the DUE do not frequently result in serious harm, injury or impairment to the patient. o Output from ongoing review of incidents and adverse events (if any) related to the DUE and similar devices confirms a low incidence of clinical complications or other effects linked to misdiagnosis caused by product's error.
	Incidence with SW System not > documented incidence with similar devices	Clinical	- Incidents and adverse events (if any) related to the DUE and linked to misdiagnosis caused by user's error in the DUE do not result in serious harm, injury or impairment to the patient.

Misdiagnosis caused by user's errors			○ No serious clinical complications or other effects linked to misdiagnosis caused by user's error in the DUE are observed in the clinical studies and registries performed with the DUE. - Incidents and adverse events (if any) related to the DUE and linked to misdiagnosis caused by user's error in the DUE do not frequently result in serious harm, injury or impairment to the patient. ○ Output from ongoing review of incidents and adverse events (if any) related to the DUE and similar devices confirms a low incidence of clinical complications or other effects linked to misdiagnosis caused by user's error in these systems.
Patient's privacy and data security	Incidence with SW System not > documented incidence with similar devices	Clinical	- Incidents and adverse events (if any) related to the DUE and linked to patient's privacy and data security issues in the DUE do not result in serious harm, injury or impairment to the patient. ○ No serious clinical complications or other effects linked to patient's privacy and data issues in the DUE are observed in the clinical studies and registries performed with the DUE. - Incidents and adverse events (if any) related to the DUE and linked to patient's privacy and data security issues in the DUE do not result in serious harm, injury or impairment to the patient. ○ Output from ongoing review of incidents and adverse events (if any) related to the DUE and similar devices confirms a low incidence of clinical complications or other effects linked to patient's privacy and data security issues in these systems.

Recommendations that could lead to a serious adverse event	Naevia medical does NOT provide recommendations that could lead to a serious adverse event shall be identified as patient safety risks, including: - Possibility of death. - The need for a medical or surgical intervention that would not otherwise be necessary. - Omission of critical recommendations that could adversely affect the patient's prognosis	Clinical	- An observational, study consisting on a clinical validation of a CDSS applied to retrospective clinical cases of patients with valvular heart disease; must determine whether Naevia medical, when faced with real clinical cases, issues inappropriate recommendations that may represent a risk to patient safety. Recommendations that could lead to a serious adverse event shall be identified as patient safety risks, including: o Possibility of death. o The need for a medical or surgical intervention that would not otherwise be necessary. o Omission of critical recommendations that could adversely affect the patient's prognosis.

The benefit-risk balance is focused on the assessment of:

- History of safe use of similar devices.
- The residual clinical risks when using the device as intended by the manufacturer should not be higher than those already described in the literature and post-commercialization experience for similar devices already available on the market.
- The preclinical and clinical studies performed for the DUE following the parameters included in the applicable standards are available and will support the safety profile of the DUE.
- A market experience search regarding the history of safe use of similar devices will be performed and will be detailed in the Literature Search Report in order to identify the possible clinical risks arising from the use of similar products that are already available in the market.

The clinical benefits expected by the use of the DUE are detailed in Section 7 of this Clinical Evaluation Plan.

Possible risks arising from the use of the device have been identified in the Risk Management Report and the benefit/risk analysis related are detailed in sub-section 10.1 of this Clinical Evaluation Plan.

12. Benefit-risk issues relating to the specific components – use of pharmaceuticals, non-viable animal, or human tissue.

The device under evaluation does not include pharmaceuticals, medicinal products or non-viable animal or human tissue.

13. Required level of clinical evidence

As outlined previously, literature search and review shall be conducted to establish the state of the art. Literature search is also expected to yield up-to-date information concerning current alternatives and standard of care.

Taking into account the characteristics of the device and its intended purpose, it is expected that robust, published clinical data concerning similar devices shall be found and can be obtained in order to incorporate it fully into the technical documentation. Equivalence with one of these similar devices is anticipated enabling the leveraging and use of this data to establish sufficient clinical evidence. Scientific quality of the available data shall be assessed during the appraisal stage of the clinical evaluation. Appraised datasets that qualify as clinical data shall be the basis for analysis to determine if the available information provides sufficient clinical evidence.

In order to define the required level of clinical evidence, reference is taken from what is established in Appendix III of Guidance document MDCG 2020-6. Note that this guidance document refers to legacy devices (medical devices previously CE marked under Directives 93/42/EEC), thus it is only considered to establish the hierarchy of the clinical evidence. The level of clinical evidence found may be ranked (e.g., Rank 1 to Rank 12 where Rank 1 are results of high-quality clinical investigations, Rank 4 are Outcomes from studies with potential methodological flaws but where data can still be quantified and acceptably justified, and Rank 12 are Preclinical and bench testing / requirements to standards) and are likely to vary between:

- **High Level (Rank 1 to Rank 4):** Includes data sourced from clinical investigation(s) with the DUE itself or data sourced from other clinical studies with the DUE itself where the data can be quantified, and it is acceptability justified.

- **Medium Level (Rank 5, 6):** Includes data sourced from clinical investigation(s) or other clinical studies with a device demonstrated to be equivalent to the DUE.

- **Low Level (Rank 7, 8, 9):** Includes data sourced from curated complaints and vigilance data or structured, proactive PMS data pertaining to the DUE. Case reports on the DUE. Clinically relevant information pertaining to similar (but non-equivalent) devices.

- **Non-clinical (Rank 10, 11, 12):** Evaluation of the state of the art based on data from similar devices. Compliance to non-clinical elements of common specifications. Simulated use, animal or cadaver testing involving end-users. Pre-clinical and bench testing showing compliance to standards.

For this device, taking into account the device risk class, characteristics and intended purpose, it is anticipated that HIGH level clinical evidence can provide enough specific information for conformity assessment purposes.

14. Clinical development plan (CDP)

The purpose of this section is to establish a plan indicating the progression of our clinical development as referred to in Annex XIV Part A of MDR with an indication of milestones and a description of potential acceptance criteria.

Any clinical investigation envisaged shall be planned and conducted in line with regulatory and ethical requirements applicable in the country where the investigation is to be performed and in accordance with good clinical practice as set out in standard ISO 14155 (ISO/TC194 2021).

Overview

This is the first Clinical Evaluation Plan according to the Regulation (EU) 2017/745 on medical devices, since the DUE, NAEVIA MEDICAL, has not been on the market before (2017).

Clinical Investigations Undertaken

The following tables summarize the clinical investigations that have been placed for the DUE:

Main clinical investigation

Title	Clinical validation study of naevia medical, a decision support tool for valvular heart disease
Registration number	ClinicalTrials.gov ID NCT06392464
Start and End	2024
Publication	*Pending*
Design	pre-test-post-test of a randomly assigned group, using a longitudinal repeated measures approach and retrospective validation
Duration	3 months
Centres	Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS)
Sponsor	DILEMMA SOLUTIONS SL
Main objective	Demonstrate that the use of the naevia medical CDSS significantly increases appropriate recommendations based on clinical practice guidelines, and decreases the number of inappropriate recommendations received by the patient, compared to conventional management.
Device under investigation	Naevia medical
Number of participants	101

Title	Clinical validation study of naevia medical, a decision support tool for valvular heart disease
Inclusion criteria	Retrospective clinical retrospective cases of patients with valvular heart disease will be selected in a stratified randomised manner from among: (i) patients presented at a medical-surgical session. ii) patients from the monographic consultation of valvopathies. Inclusion criteria: - Clinical cases of patients randomly selected from among those presented during the year 2022 in medical-surgical session with the main diagnosis of aortic valvular stenosis, aortic insufficiency, mitral stenosis and mitral insufficiency (greater than moderate grade). Randomisation will be stratified ensuring that 50% come from the medical-surgical session. - Clinical cases of patients randomly selected from clinical records of the Valvopathy Consultation seen in 2022 with the main diagnosis of aortic stenosis, aortic insufficiency, mitral stenosis and mitral insufficiency (major degree). mitral regurgitation (greater than moderate grade). Randomisation will be stratified by ensuring that at least 40% of patients have aortic valve disease and 20% have mitral valve disease. - Age ≥18 years.
Exclusion criteria	- Subjects under 18 years of age. - Inability to anonymise the case. - Clinical cases of valvular heart disease involving complex congenital heart disease. - Clinical cases that do not meet the minimum set of data necessary for decision-making. - Clinical cases with a principal diagnosis other than valvular heart disease. - Presence of bacterial endocarditis.
Primary and Secondary Outcomes	It is considered clinically beneficial to increase the number of appropriate recommendations by 15% over the recommendations generated with general management without the support system. The baseline/pre-test value is the number of appropriate recommendations based on clinical practice guidelines during conventional management (without CDSS). Inappropriate recommendations as judged by the committee of expert assessors during conventional management will also be collected. The post-intervention/post-test value is the number of appropriate guideline-based recommendations after activation of the naevia medical decision support system. Inappropriate recommendations in the judgement of the committee of assessors during CDSS management will be collected. To calculate the percentage increase between two values we will use the following formula: Percentage increase = (Post-intervention value-Baseline value/Baseline

Title	Clinical validation study of naevia medical, a decision support tool for valvular heart disease
	value) ×100%.
Protocol reference	*TD01-06-1C-06-02 CIP_NCT06392464*

Other supporting studies/registries

Title	Development of knowledge-based clinical decision support system for patients included in colorectal screening program
Registration number	2020-640-1
Start and End	Start: September 1, 2020 End: October 30, 2020
Publication	Lorenzo-Zúñiga V, Bustamante-Balén M, Pons-Beltrán V, Peña-Gil C. Development of knowledge-based clinical decision support system for patients included in colorectal screening program. Gastroenterol Hepatol. 2022;45(6):419-423. doi:10.1016/j.gastrohep.2021.05.01 (Lorenzo-Zuniga, Bustamante-Balen et al. 2022)
Design	Retrospective cohort study
Duration	2 months
Centres	Hospital Univesitari I Politecnic La Fe- Valencia
Sponsor	Hospital Univesitari I Politecnic La Fe- Valencia
Main objective	To develop a K-CDSS for the management of CRC screening patients, and to evaluate its efficacy.
Device under investigation	DILEMMA Solutions Platform© ((naevia medical)
Number of participants	69
Inclusion criteria	Patients at a large referral center in Spain who underwent colonoscopy under CRC screening program.
Exclusion criteria	Patients with a personal history of CRC, inflammatory bowel disease (IBD), hereditary polyposis syndromes, prior colectomy, Boston Bowel Preparation Scale (BBPS) < 5 or an endoscopic report of poor preparation quality (inadequate visualization of polyps < 5 mm), incomplete colonoscopy (defined as failure to intubate the cecum), and polyp retrieval failure.
Primary Outcomes	The degree of agreement between expert physicians and nurses using a CDSS based on colonoscopy data was very high. There were no differences in erroneous recommendations with PoliCare CDSS (Kappa value 1.0).

Title	Development of knowledge-based clinical decision support system for patients included in colorectal screening program
Protocol reference	*TD01-06-1C-06-06 CIP_2020-640-1*

Title	Development and pre-clinical evaluation of an advanced decisionsupport system for hypertrophic cardiomyopathy clinical management
Protocol code	*2021-2-19-HCUVA*
Publication	*NA*
Design	Observational, multicenter study for the validation of a digital clinical decision support tool (CDSS) applied to clinical cases of patients with hypertrophic cardiomyopathy.
Duration	9 months
Centres	Hospital Virgen de la Arrixaca
Sponsor	Amicus Therapeutics.
Main objective	To evaluate the degree of concordance between management decisions of experts (Standard Output) versus non-experts supported by the CDSS (non-experts+CDSS output), in patients with HCM.
Device under investigation	Naevia medical
Number of participants	4101 rules (algorithms) covering HCM and related problems (heart failure, atrial fibrillation, valvular heart disease, arterial hypertension, dyslipidaemias, diabetes, coronary syndromes) were coded in the CDSS and were evaluated in 60 cases (internal validation).
Inclusion criteria	Patients evaluated consecutively with a main diagnosis of hypertrophic cardiomyopathy in which the available clinical information is considered sufficient for the generation of diagnostic and therapeutic recommendations.
Exclusion criteria	Absence of relevant clinical information for medical decisions. Problems for case anonymization.
Primary Outcomes	External validation phase 1: For each question (n=42), the experts (n=10) provided a total of 56 answers (28 with and 28 without CDSS) and non-experts (n=9) provided 62 answers (31 with and 31 without CDSS), to sum a total of 2184 individual questions (42 per case in 26 cases evaluated twice) and 4956 answers (including 248 answers that were considered the references, and 4708 answers to be evaluated). In experts, the number of right answers improved with CDSS on from 1020 to 1032 (1.1%) and the number of wrong answers decreased from 156 to 144 (7.6%) (p=0.46). In non-experts, the number of right answers improved from 1074 to 1094

Title	Development and pre-clinical evaluation of an advanced decisionsupport system for hypertrophic cardiomyopathy clinical management
	(1.9%) and the number of wrong answers decreased from 228 to 208 (8.7%) (p=0.29). External validation phase 2: 21 additional cases were evaluated by 4 experts (2 with, 2 without CDSS) and 4 non-experts (2 with, 2 without CDSS). The answers showed low concordance both inter and intra group, with and without CDSS (kappa <5 for all evaluated answers).
Protocol reference	*TD01-06-1C-06-01 CIP_2021-2-19-HCUVA*

Additionally, Naevia Medical's platform has been or is being used in other significant registries, such as:

- The "REDMIO20: Spanish Registry of Dilated Cardiomyopathy due to RBM20 Gene Mutation," a multicenter registry coordinated by Dr. Eduardo Villacorta from the Salamanca University Assistance Complex, which included 168 cases up to December 11, 2023.
    - Protocol reference: *TD01-06-1C-06-03 CIP_REDMIO*

- The "PROCeso asistencial integrado de Estenosis Aórtica grave Sintomática (PROCEAS)" 2020/405 registry, led by Dr. Violeta González-Salvado from the Santiago de Compostela University Clinical Hospital, with 991 cases of aortic stenosis registered up to December 11, 2023.
    - Protocol reference: *TD01-06-1C-06-04 CIP_PROCEAS*

Ongoing Clinical Investigations

- **Preliminary Study on Ischemic Heart Disease**: This study focuses on the "2023 ESC Guidelines for the management of acute coronary syndromes". As a result of an agreement with the European Society of Cardiology, simulations of 731 cases have been created up to December 11, 2023, along with 22 representative cases. This study is especially important to validate the system's capability in managing patients with ischemic heart disease, a highly prevalent area in cardiovascular medicine.
    - Protocol reference: *TD01-06-1C-06-08 CIP_ESC Guidelines. Preliminary Study on Ischemic Heart Disease*

- **Case registry and quality indicators in cardiac rehabilitation centers**:
    - Protocol reference: *TD01-06-1C-06-05 CIP_ReCardio*.

Future investigations / PMCF

PMCF Studies will be performed with the aim of potentially widen the indications of Naevia medical.

- **Preliminary Study on Breast Cancer:** Studies based on the "ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up" for early breast cancer have been conducted. This study is crucial to ensure that the Naevia Medical system can effectively manage breast cancer cases, following the established clinical guidelines.
- **Diabetes Mellitus**: Validation study for the management of type 2 diabetes: Based on the ADA (American Diabetes Association) guidelines.

Active Vigilance and Monitoring

After the device is placed on the market, strategies, and methods to systematically collect, summarize, and assess post-market clinical data shall be defined in the specific Post-market Surveillance (PMS) plan, as well as in the Post-market Clinical Follow-up (PMCF) Plan.

The purpose is to proactively collect and evaluate clinical data from the use in humans of the device within its intended purpose with the aim of confirming the safety and performance throughout the expected lifetime of the device, of ensuring the continued acceptability of identified risks and of detecting emerging risks based on factual evidence.

Feedback information from PMS and PMCF shall be evaluated to determine any necessary product changes or improvements.

The impact of any proposed changes or improvements shall be reviewed and considered in the annual Risk Management and Clinical Evaluation reviews. Also, design changes shall be evaluated for impact on the Certificate(s) issued by the Notified Body. All such changes shall be controlled and documented updating the corresponding sections of this Technical Documentation.

15. References

- MDCG 2020-6 Guidance on *"Clinical evidence needed for medical devices previously certified under Directives 93/42/EEC and 90/385/EEC (legacy medical devices)"*
- MDCG 2020-5 Guidance on "Clinical evaluation – Equivalence. A guide for manufacturers and notified bodies"
- MEDDEV 2.7/1 rev.4 (2016) *"Clinical evaluation – A guide for manufacturers and notified bodies under Directives 93/42/EEC and 90/385/EEC"*

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