Investigational Medical Device Dossier (IMDD)

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AUTHORS

Ian (Zhengru) Shen	Utrecht University z.shen@uu.nl
Michiel Meulendijk	Utrecht University m.c.meulendijk@uu.nl
Wilma Knol	UMC Utrecht w.knol@umcutrecht.nl
Lianne Huibers	UMC Utrecht
Ingeborg Wilting	UMC Utrecht
Paul Jansen	UMC Utrecht
Marco Spruit (corresponding author)	Utrecht University m.r.spruit@uu.nl

VERSION HISTORY

Version	*Date*	*Authors*	*Summary*
2.00	31/03/2016	IS *et al.*	- Initial version for review by UMCU/MTKF
2.02	12/07/2016	IS/MS	- Revision sent out to UMCU/MTKF, OPERAM
2.03	29/09/2016	MS	- Added extra risks to Annex VI: Risk management report - Marked STRIPA-specific Device Deficiencies to Annex VI - Updated reference in section 9: Shen et al. (2016) now published - Added extra section to Annex VI

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Abbreviations

ADE	Adverse Drug Event
AIMDD	Active Implantable Medical Devices Directive
ATC	Anatomical Therapeutic Chemical
CE	Conformité Européenne
DRA	Drug-related hospital admissions
eGFR	Epidermal Growth Factor Receptor
GHTF	Global Harmonization Task Force
ICD	International Statistical Classification of Diseases
IMDD	Investigational Medical Device Dossier
MDD	Medical Devices Directive
MEDDEV	Guidance document for the interpretation of European legislation
SHIM	Structured History Taking of Medication
MREC	Medical Research Ethical Committee
STED	Summary Technical Documentation
STRIP	Systematic Tool to Reduce Inappropriate Prescribing
SHIM	Structured History Taking of Medication

1. Device description and specification

General description

The expected growth of the elderly population in the coming decades presents great challenges for public healthcare all around the world. The European demographic structure is expected to dramatically change over the coming 4 decades with almost a doubling of the population aged 65 years and older and tripling of the number of people aged over 80 years [1]. Polypharmacy, commonly defined as use of ≥5 chronic medications, by a patient, poses a significant threat among the elderly people [2, 3]. With increasing age the prevalence of multi-morbidity increases sharply contributing to undesirable levels of polypharmacy and inappropriate prescribing. Inappropriate polypharmacy can have detrimental effects especially in elderly patients for several reasons [2, 4].

- Older people are at increased risk for adverse drug events (ADEs) because of age-related changes, such as the reduction of the hepatic drug clearance and the high prevalence of renal impairment etc.
- With polypharmacy, there is an increased risk of drug-drug and drug-disease interactions.
- 'Prescribing cascades' have been described and occur when ADEs are misinterpreted as a new disease, leading to prescription of additional medications and potentially resulting in further adverse events.
- Polypharmacy is associated with poor drug compliance and other negative health outcomes, such as drug-related hospital admissions (DRAs), cognitive decline, falls, and an increased risk of hip fractures.

In order to reduce these polypharmacy problems, a structured method has been developed: the Systematic Tool to Reduce Inappropriate Prescribing (STRIP) is a drug optimization process, consisting of an anamnesis of patients' actual perceived problems and drug use, and a pharmacotherapeutic analysis [5]. It has been included in the Netherlands in a multidisciplinary guideline on polypharmacy and elderly patients [6]. Research proves that it is effective in helping final-year medical students improve their prescribing skills [7]. The method leads to a newly refined individual treatment plan, omitting superfluous drugs and adjusting dosages where applicable. The STRIP process is shown in Figure 1 [8]. These five steps are summarized as follows:

1. structured history taking of medication (SHIM) [9];
2. pharmaceutical analysis using the STRIP Assistant with the integrated STOPP/START criteria [10], advising the prescriber on the correctness of drug indications and dose, the presence of ADRs, interactions and the list of generic drugs for the prescriber to consider to replace brand named drugs;
3. decision-making of physician and pharmacist regarding the drug therapy advice to be given to patients;
4. shared decision-making with the patient, and performing the decided medication changes;
5. follow-up and revision.

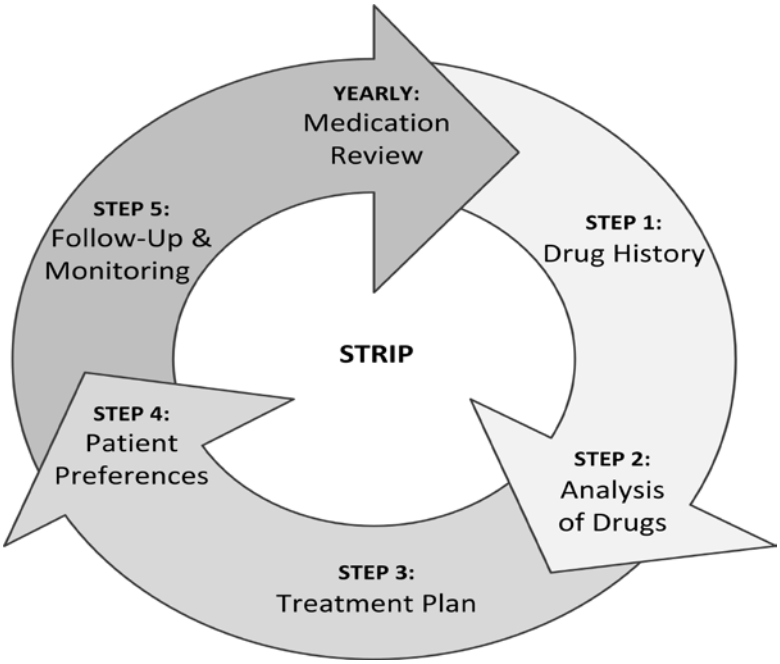

Figure 1. The STRIP process

At first, a software tool was developed to ensure that the structured medication review method STRIP is incorporated into physicians' and pharmacists' daily practice. Then the software has further developed by combining both the STRIP method and the Irish Structured Pharmacist Review of Medication (SPRM) [11] method to facilitate the most time-consuming and complex step in the process: the analysis of drugs.

The software tool, named STRIP Assistant (STRIPA), is a stand-alone web application that effectively and efficiently facilitates physicians' and pharmacists' medication review process, by optimally providing real-time suggestions during the pharmacotherapeutic analysis [5]. Based on patient's medical history it is capable of generating its context-specific advices that can either be heeded or rejected by the user. Advices can propose to start new medication, stop specific drugs, or change the dosage or frequency of a drug already used; any or all of these actions may be combined in any given advice. The knowledge used to generate STRIPA's advices is based on well-established guidelines on clinical interactions, double-medications, contraindications, dosage and dosage frequency, and specific implementations of the START- and STOPP-criteria. The application was designed as an independently invokable process, enabling the creation of an autonomous user interface free from restrictions that regularly limit plug-in applications and lead to suboptimal workflows.

Moreover, STRIPA differs from most decision support systems integrated in computerized physician order entry (CPOE) systems in terms of the way of generating advices. It is able to directly incorporate users' actions, thereby real-time updating its advices in response to users changing, adding or removing drugs. But most CPOE systems base their advices on input available at specified moments in time (e.g. upon opening a patient's health record). To ensure that only relevant advices are displayed, the rule engine was designed to incorporate context-specific characteristics, and to work with both complex and simple rules.

The intended patient population

As discussed earlier, STRIPA has developed to facilitates physicians' and pharmacists' medication review process. It will be used to support a multicenter large-scale cluster randomized clinical trial (RCT) involving research institutions or hospitals from multiple European countries: the Netherlands, Belgium, Switzerland and Ireland [12]. The RCT is the

core part of the OPERAM (OPtimising thERapy to prevent Avoidable hospital admissions in the Multi-morbid elderly) project which intends to optimize existing pharmacological and non-pharmacological therapy primarily in order to reduce avoidable hospital admissions among the elderly population aged ≥ 65 years with multi-morbidity. All the patients that are selected for the RCT are the intended patients. Moreover, the Dutch multidisciplinary guidelines on polypharmacy, which implements the STRIP method, also identify patients are eligible for a structured medication review. Therefore, the intended patient population of STRIPA is specified with the following conditions [8]:

1. over 65 years of age
2. polypharmacy (i.e. chronic use of five or more medications); and at least one additional risk factor:

Principles of operation

This section focuses on the underlying principles of operation that are embedded in STRIPA to ensure the requirements of performing effective and efficient medication reviews in cases of polypharmacy are met. Both medical and technical principles are explained in the following.

STRIP

As discussed above, STRIP lays down the foundation for the development of STRIPA and it also provides the process flow of the software. However, not all five steps of the STRIP method are covered in the software. It focuses on facilitating the most time-consuming and complex step: the pharmacotherapeutic analysis. Principles or rules includes:

1. structured history taking of medication (SHIM)
2. STOPP/START criteria, advising the prescriber on the correctness of drug indications and dose, the presence of ADRs,
3. interactions and the list of generic drugs for the prescriber to consider to replace brand named drugs
4. standardized reporting template for better communication

Rule-based decision making

STRIPA has been designed and developed as a rule-based decision support system [5]. The software relies on rules with a varying degree of complexity. The medication review domain could be modelled using three distinguishable types of rules: those based on atomic formulae, conjunctive compound formulae, and disjunctive compound formulae. Atomic formulae depend on a single condition only, containing no deeper propositional structure. Compound formulae, in contrast, do contain logical connectives to incorporate multiple conditions. While conjunctive operators require several conditions to be satisfied before a consequence is implied, disjunctive operators require only one of several conditions to be met. These types of rules have been implemented in STRIPA's rule engine; the ability to incorporate multiple types of rules is one of the characteristics which sets STRIPA apart from other decision support systems in primary care. Examples of each type of rules are shown in Figure 2 [5].

The atomic rule, of which hundreds of thousands of possible variations exist, was modelled by creating a single rule that could be triggered by any combination of objects validating the condition. Rule (2) in Figure 2 illustrates how this principle works. Any two drugs are checked for potentially dangerous clinical interactions in the database. If a match is found, an advice is created recommending the user to remove either one of the conflicting drugs.

The atomic rule, of which hundreds of thousands of possible variations exist, was modelled by creating a single rule that could be triggered by any combination of objects validating the condition. Rule (2) in Figure 2 illustrates how this principle works. Any two drugs are

checked for clinically relevant interactions in the database. If a match is found, an advice is created recommending the user to remove either one of the conflicting drugs.

The more complicated conjunctive compound rules, which depend on several conditions, were modelled independently. A table format was used to allow for more convenient correcting and editing by members of the expert panel, which was later automatically converted into code. Rule (3) in Figure 3 illustrates the working of a complex rule: the suggestion of adding a proton pump inhibitor, dependent on patients' age and their use of NSAIDs (non-steroidal anti-inflammatory drugs) and SSRIs (selective serotonin reuptake inhibitors), corticosteroids, or anticoagulants. Only if all conditions are satisfied (including, obviously, the current lack of a proton pump inhibitor) a suggestion is made.

Finally, some rules can be triggered by several (combinations of) conditions. Often, these rules have a preference for one (combination of) conditions over another; a more precise measurement is usually preferred over a more generic diagnosis. Rule (2) in Figure 3 presents an example of such a disjunctive compound rule which can be activated through several ways: recommending the addition of antihypertension drugs in case a patient suffers from untreated hypertension. Ideally, hypertension is determined by one's systolic blood pressure being higher than 160 mmHg. However, if this value is unavailable, diagnoses indicating hypertension are considered. In either case, a suggestion to add antihypertension drugs is given.

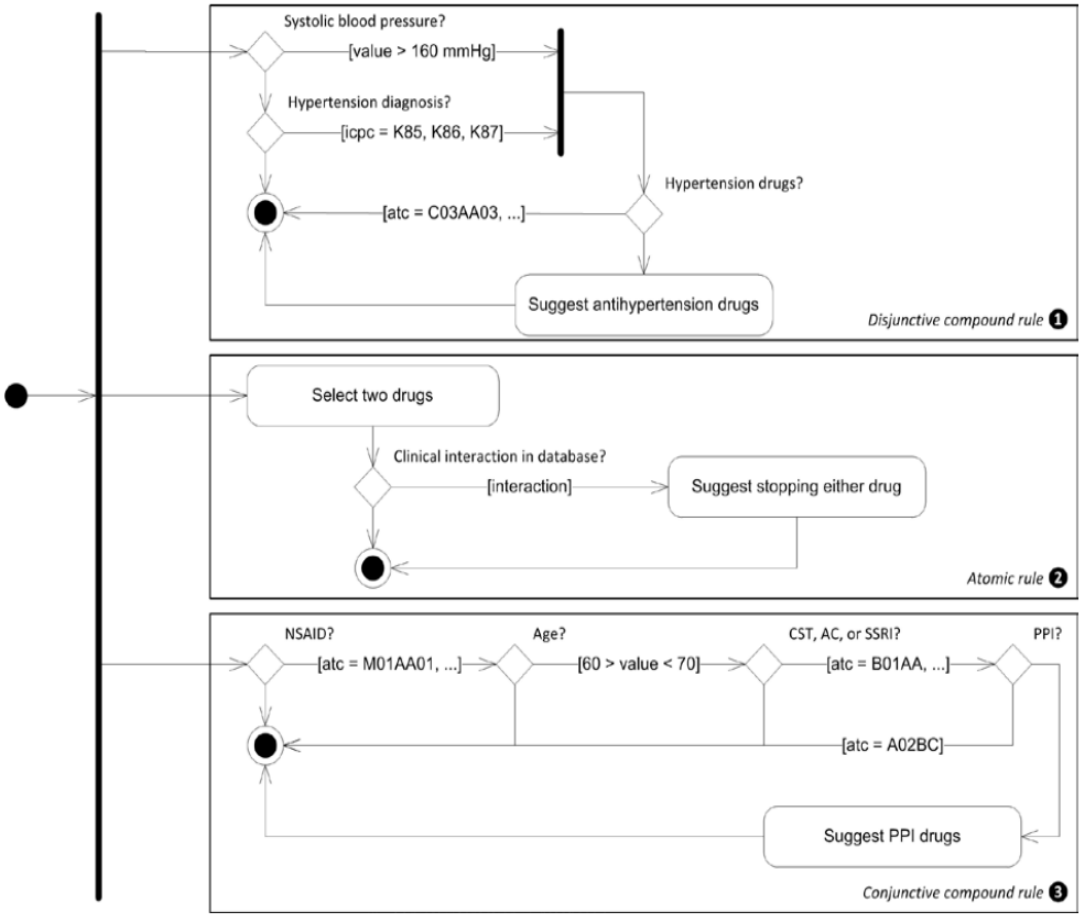

Figure 2. UML Activity Diagram depicting rules suggesting addition or discontinuation of drugs, if necessary conditions are satisfied.

Device classification and the applicable classification rule

Device classification

General medical devices and related accessories must be classified into one of four classes, which are based on the perceived risk of the device to the patient or user. The classification of a device determines the conformity assessment options that are applicable to the device, with higher risk devices undergoing higher levels of assessment [13].

Class	Type
I	Low risk
IIa	Medium Risk
IIb	Higher Risk
III	Highest Risk

Table 1. Medical devices classification

Classification rules

There are eighteen rules outlined in Annex IX of Directive 93/42/EEC and related Regulation that lay down the basic principles of classification. In the Rev. 8 of the MED DEV guidance 'MED DEV 2.4/1 Guidelines for the Classification of Medical Devices, these rules are further explained and descriptive examples are provided. The eighteen rules are subdivided into four groups as follows [14]:

Rules	Device
Rules 1–4	Non-invasive Devices
Rules 5–8	Invasive Devices
Rules 9–12	Active Devices
Rules 13–18	Special rules e.g. devices containing tissue of animal origin, drug-device combinations

Table 2. Groups of classification rules

Annex IX and related guidance documents provide a comprehensive description of a number of key characteristics that must be considered to correctly classify a device. According to the definition of active medical device, stand-alone software is considered to be an active medical device. Therefore, STRIPA is an active medical device. Rules that are applicable to active medical devices are rules 9, 10, 11 and 12. Figure 3 represents a visualization of these rules. The MED DEV 2.4/1 gives a general explanation with examples for each rule.

As depicted in Figure 3, rules 9, 10 and 11 are first checked in accordance with the characteristics of STRIPA [15]. Considering its clinical purposes, both rules 9 and 10 are not satisfied. In addition, since STRIPA only provides prescription recommendations to physicians or pharmacists who will make the final decision on whether recommendations are accepted or not, rule 11 does not apply to the software. Therefore, STRIPA is considered to be a class I medical device.

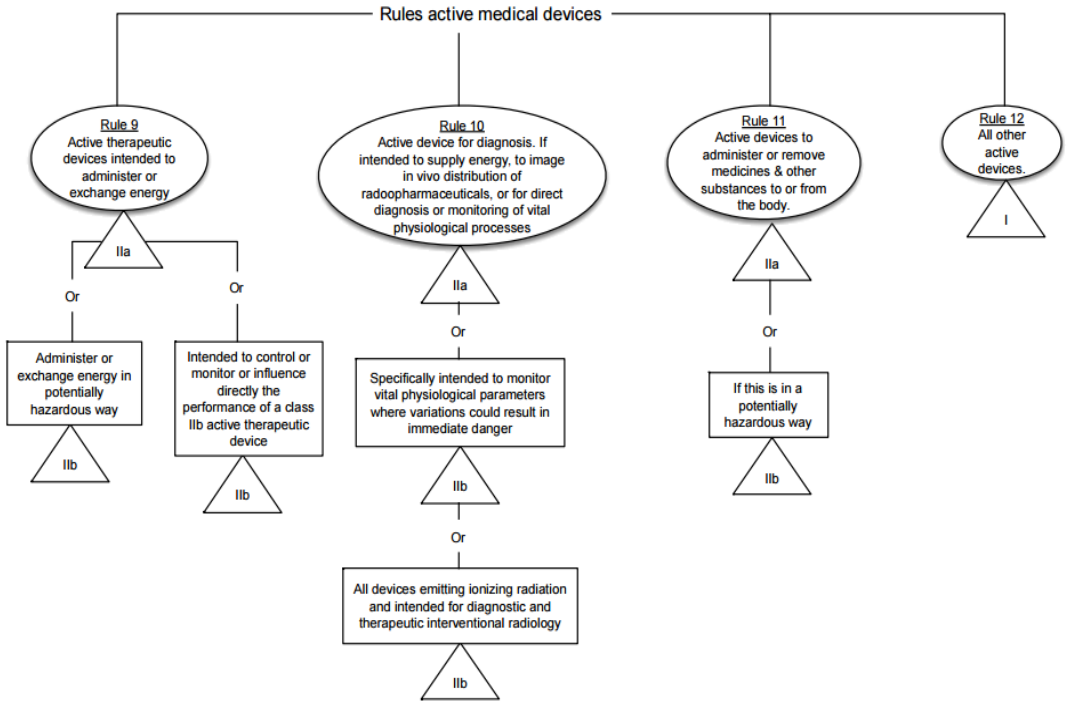

Figure 3. Decision map of classifying active medical devices

A list of features

General Features List

1. Input
   Patient data required for the analysis can be inserted in STRIPA in standardized formats (such as ICPC, ICD10, ATC), enabling easy interoperability with third-party systems.
   Decision rules come from a set of clinical guidelines (e.g. START / STOPP-criteria, relevant clinical interactions) and are verified by physicians.
2. Output
   After analysis, new data can be downloaded in a variety of formats. These either maintain the standard structures mentioned above, which enable interoperability with third-party systems, or they take the form of reports optimized for human readability.
3. Customization
   The software supports a wide variety of configurations, which can all be invoked by configuring the database to which it is connected. Through this modularization, different sets of a.o. decision rules, medication lists, and interaction databases can be used [5].
4. Security
   The federated database architecture ensures that sensitive data is stored in databases specific to each trial site. The federated, centralized, database only stores anonymous logs. Patient data in the trial databases is stored pseudonymized; identifiable information is saved on local network drives within the trial hospitals. Physical independence of the local file system prohibits unauthorized access and use of locally collected private patient data [16].
5. Usability
   In designing the user interface for STRIPA, the aim was to create an application that had the potential to be accessed through different mediums (i.e. both PCs and mobile devices). After designing an initial wireframe version based on interviews with medical

experts and potential users, a prototyping process using prototypes of increasing fidelity was used to refine it. Early prototypes of the application were used in test sessions, where users were invited to comment on its usefulness and user-friendliness. Their remarks were used to further improve the user interface [17].

6. Cross-browser support

   STRIPA has been developed and tested with cross-browser compatibility in mind. It runs on various browsers that are commonly used nowadays: Internet Explorer, Google Chrome and Mozilla Firefox.

Novel Features

During analysis, the software system generates real-time advice, incorporating the user's current actions [5]. Advice is based on a set of clinical guidelines (e.g. START / STOPP-criteria, relevant clinical interactions), best practices (e.g. common indications), and, most importantly, a patient's medical data. In response to advice(s) generated by the software, users will change, add or remove drugs from a patient's prescription, which consequently updates the patient's medical data. STRIPA is able to directly incorporate these users' actions, thereby real-time updating its advices in response to users changing, adding or removing drugs.

A description of the accessories, other medical devices and other products that are not medical devices, which are intended to be used in combination with it

N/A

A complete list of configurations

STRIPA has been developed to function in a predetermined back-end environment. Table 3 below details the required software and their versions.

Technical Aspect	Version Requirements
Server	Linux/Windows
Host	Apache Tomcat v7.x
Database	MySQL
Java	7.x
jQuery	1.8.2
requireJS	2.1.19
Talend	5.6.2

Table 3. Technical configurations of back-end environment

STRIPA is a web application that has been developed to run from a browser. While it has been designed to function in as many front-end environments as possible, the recommended configuration detailed below is guaranteed to work.

Technical Aspect	Version Requirements
OS	Windows ,8,10
Browser	Internet Explorer 10+

Table 4. Technical configurations of front-end environment

The data used in STRIPA's knowledge base comes from a variety of sources. These are partly dependent on the country in which the data is to be used. Table 5 below gives an overview of the characteristics of the various data sources that have been implemented.

Supplier	Database / Standard	Scope	Format	Country	Languages
Z-Index	G-Standard	Medications, Clinical Interactions	Fixed Width	Netherlands	Dutch
RIVM	ICD-10	Episodes	XML	Netherlands	Dutch
APB	Delphi-Care	Medications, Clinical Interactions	Fixed Width	Belgium	French, Dutch
FOD	ICD-10	Episodes	CSV	Belgium	French, Dutch
HCI Solutions	INDEX	Medications, Clinical Interactions	XML	Switzerland	German, French
DIMDI	ICD-10	Episodes	XML	Switzerland	German
HelixHealth	Safescript	Medications, Clinical Interactions	Fixed Width	Ireland	English
WHO	ICD-10	Episodes	XML	Ireland	English
MedDRA MSSO	MedDRA	Adverse Events	CSV	Netherlands, Belgium, Switzerland, Ireland	Dutch, French, German, English
Regenstrief	LOINC	Measures, Laboratory Tests	CSV	Netherlands, Belgium, Switzerland, Ireland	Dutch, French, German, English

Table 5. Overview of the characteristics of the various data sources

The table below gives an overview of which configurations were implemented in the various national trial sites.

	Ireland	Netherlands	Belgium	Switzerland
Language	English	Dutch	French	German
ICD-10 Version	WHO	RIVM	FOD	DIMDI
Medical DB	SafeScript	G-Standard	DelphiCare	INDEX
START/STOPP Versions	2.0	2.0 Customized	2.0 Customized	2.0

Table 6. National configurations

The key functional features

A federated database system

For STRIPA.EU a federated database system was developed instead of a data warehouse for a number of reasons. The database in each country is not a subset of a centralized database, but each contains all data necessary for the application and takes nothing from the centralized

one. Patient health records collected locally need to remain under the control of the local authorities for the sake of privacy and security. Only collected research data in each country is allowed to be transferred into the centralized database. A federated database system grants autonomy to the database in each country, which guarantees national databases can be configured according to local customizations [16].

Figure 4 depicts the integration architecture that was designed for STRIPA.EU. It is a federated database system which is composed of a federated database and a number of autonomous national databases. As shown in the figure, each country has its own national database, and private patient data is extracted and saved in local file system within hospitals. National databases are autonomous and independent of each other, and store their locally configured decision rules and medical data. The federated database stores metadata for data in all countries and gathers logs for research purposes.

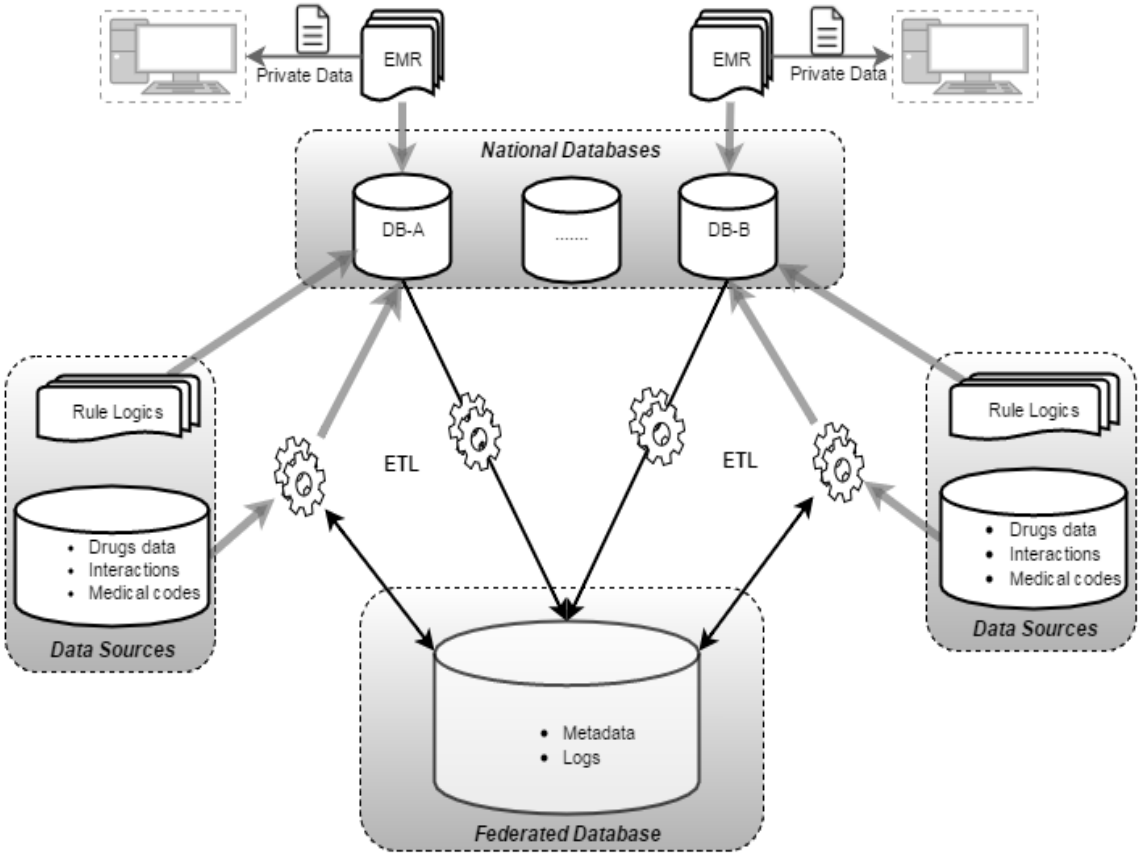

Figure 4. Integration Architecture of STRIPA.EU

Automated ETL processes

The development of the software is supported by automated ETL processes that have been constructed to have external data sources loaded into databases. Even though these ETL processes are not included as components of the software itself, they lay down the groundwork for the successful implementation of STRIPA. There are a number of challenges ahead when it comes to constructing a successful ETL implementation: 1) significant dissimilarity between external data sources and target data structure; 2) external data sources are encoded in diverse formats, including CSV, fixed width and XML; 3) ETL needs to be autonomous, preferably just a click away. A powerful open source tool (Talend Open Studio for Data Integration) has been used to operationalize ETL processes. It is capable of tackling a variety of data formats and its graphic interfaces make ETL easier to follow and can thus be evaluated by non-IT experts [16].

Functional modularization

From a functional viewpoint, the application's key features are accommodated in three modules: user manager, dashboard and analyzer. Figure 5 shows what each of these systems consists of and how they are related. In the following sections each of these features is elaborated upon [5].

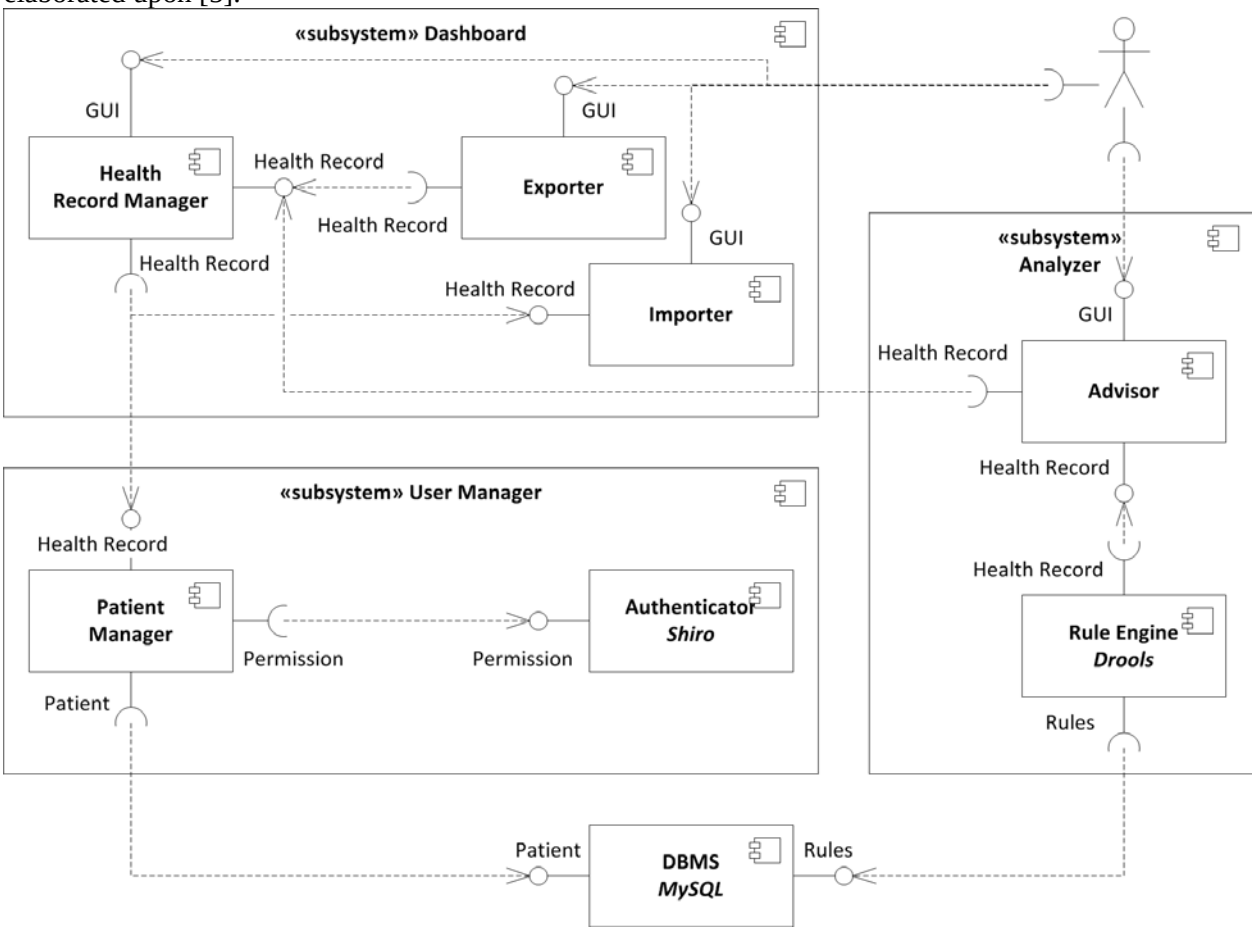

Figure 5. UML Component Diagram depicting STRIPA's modules

The User Manager sub system has two primary functions; it manages the current user's session and his or her specific permissions, and it supplies the rest of the system with requested patient data. Acting as a gatekeeper, every request is authenticated before it is executed and its results are returned to the calling function.

The Dashboard sub system provides a user interface for recording the results of patients' anamneses. An anamnesis typically provides an individual's diagnosed diseases, complaints, prescribed drugs, self-medication, and recorded measurements. These values are either obtained or validated through communication with the patient, but physicians' and pharmacists' information systems can serve as initial sources of patient data. The Importer component provides users the ability to upload health records from third-party sources. These can then be edited through the user interface provided by the Health Record Manager component.

Finally, the Analyzer sub system provides a user interface for performing the pharmacotherapeutic analysis. The changes made to the health record during the process are sent to the Rule Engine component, which holds them in working memory. The appropriate rules are then executed and its results returned to the Advisor component, which shows them to the user. The user is free to heed or reject the advices provided by the rule engine. After completing an analysis, a patient's medical history is updated by the Health Record Manager

component, which in turn updates the patient data in the database. When required, the analysis' results or complete health record can be exported to a third party application through the Exporter component.

Dimensions of the medical device

N/A

A description of the materials incorporated into key functional elements and those making either direct contact with a human body or indirect contact with the body

N/A

2. Previous generations of the device and similar devices

The manufacturer's previous generation(s) of the device

The first version of STRIP assistant (STRIPA) is a web application that was built to help primary care practitioners and pharmacists to perform medication reviews for polypharmacy patients [5]. Its features were largely similar to that of the STRIPA version presented here, but it was developed for the research purposes and was used mainly within the scientific settings. Its knowledge base consisted of the first version of the START- and STOPP-criteria, and the Dutch clinical database G-Standaard.

STRIPA 1.0 was evaluated in both controlled environments and in practice. In an online experiment, forty-two physicians were asked to optimize two comparable medical records of polypharmacy patients, one in their usual manner and one using STRIPA. Medication optimization significantly improves with the STRIP Assistant. Appropriate decisions increase from 58% without help to 76% with the STRIP Assistant. Inappropriate decisions decrease from 42% in the unassisted case to 24% in the assisted one. Participants do, however, spend significantly more time optimizing medication with the STRIP Assistant (24 minutes) than without it (13 minutes) [17].

To determine if the system performs well in real life, and if its efficiency increases when it is used over a longer period of time, a case study was conducted. Four expert teams consisting of a physician and a pharmacist conducted structured medication reviews on patients in 13 general practices located in Amsterdam, the Netherlands. During thirteen months, the expert teams performed 261 medication reviews. Analysis of the acquired data shows that the amount of time users need to perform medication reviews decreases significantly as they gain experience over time; during the first half of the study they needed 15.7 minutes on average to conduct one review, while during the second half the mean time had decreased to 10.7 minutes [18].

Similar devices available on the local and international markets

N/A

3. Label(s) and instructions for use

Label(s) on the device and its packaging

As a stand-alone software for a clinical trial at this moment, the device does not own an official label like many other medical devices. However, necessary information that gives a proper description of the software is shown in its interfaces. Therefore, screenshots of the software will be attached in the Annex I.

Instructions for use

1. The patient information obtained in the SHIM is entered into the STRIPA by either the research physician or the research pharmacist.
2. In the trial management Excel sheet (available per trial site) a new patient is added, whom is assigned a unique identifier by the STRIPA server.
3. The user registers personally identifiable information (a.o. name, gender, age) of the patient in this Excel sheet at the corresponding row.
4. The user visits STRIPA, supplying his login credentials and the new patient's unique identifier.
5. The user enters the patient information required for the pharmacotherapeutical analysis in STRIPA. This comprises diseases, medications, complaints, measurements, and scores, but no personally identifiable information (e.g. name).
6. Information is entered as the closest match between the recorded data and the provided list of standard terms. Available standard terminologies include ATC, ICD10, LOINC, and MedDRA.
7. In the case of medications, dosage amount is entered in meaningful units rather than package units (e.g. 20 milligrams rather than 1 tablet). Frequency is entered and, if available, duration.
8. In the case of diseases, starting date is entered if available.
9. In the case of measurements, outcome is entered and, if available, execution date.
10. The STRIPA analysis is deployed by either the research physician or the research pharmacist.
11. In the first step of the analysis, the user drags medications to diseases for which they have been indicated.
12. In the second step, the user checks the health record for undertreatment. STRIPA generates warnings and advice based on the START-criteria, to which the user responds.
13. In the third step, the user checks the health record for overtreatment. STRIPA generates warnings and advice based on the STOPP-criteria and on rules pertaining to double medication, to which the user responds.
14. In the fourth step, the user drags complaints to medications that have caused them. STRIPA generates advice for these decisions based on the PROTECT Adverse Drug Reactions database.
15. In the fifth step, the user checks the health record for clinical interactions. STRIPA generates warnings and advice based on decision rules pertaining to drug-drug interactions, to which the user responds.
16. In the sixth step, the user checks the health record for dosage (frequency) adjustments. STRIPA generates warnings and advice based on decision rules pertaining to renal functioning, to which the user responds.
17. The user finishes the analysis and generates the report containing the proposed changes in the medication.

4. Quality systems for design and manufacturing of the medical device

Since the software was designed and developed by a group of researchers and intends to be used for the purposes of research, there is no complete quality systems for design and manufacturing of the medical device. However, throughout the design and development of STRIPA, quality control is implemented to ensure the software meet quality standards. Moreover, scientific research methods are adopted to guide the design and development process. In the following both quality control approach and scientific research methods are explained.

Quality control approach

Quality control approach is described with regard to EN ISO 13485 [23], the international standard used by nearly all manufacturers of medical devices.

Quality policy and quality objectives

STRIPA has been created by a team of IT researchers and clinical experts who aim to develop an effective and efficient decision support tool for medication reviews in polypharmacy. The team is committed to deliver a superior quality software that meet applicable regulatory, statutory, and clinical requirements by adhering to an effective quality control approach and following solid research methods.

The quality objectives are to:

- function as a team in our efforts to deliver a successful product
- facilitate medication review process in physician's or pharmacist's daily practice
- provide proper training and extensive documentations for users
- ensure effective maintenance is provided when necessary

Quality control actions

To keep the product quality of STRIPA, a number of actions were taken to during the design, development and maintenance of the system. Here a list of crucial ones are as follows:

- The system is designed together with field experts, namely physicians and pharmacists. At first, prototype was created by developers based on clinicians' requirements. Then the prototype was evaluated by these clinicians. Through multiple rounds of iteration, requirements of physicians and pharmacists are correctly understood by developers and well-represented within the design of the system.

- In the development phase, proper planning is constructed in the first place to establish documented procedures for controlling and monitoring the development of the system.

- Data inputs quality plays a crucial role in the development phase. To begin with, decision rules, such as START/STOPP criteria, are validated by physicians. Furthermore, ETLs that have been developed to extract medication data, including drugs, drug-drug interactions and dosage, are also able to be used to check data accuracy and consistency.

- Our team determines the monitoring and measurement to be undertaken and the monitoring and measuring devices required to provide evidence of conformity of product to determined requirements. In particularly, studies have been conducted to investigate efficacy of the system in daily clinical practices [17, 18].

- To monitor the performance of the system and further understand the users, user logs will be collected for further user behavior analysis [16]. These analysis results will also be used as inputs for product improvement.

- From a perspective of project management, documentations are required.

5. Manufacturing processes

Manufacturing processes contains information that shows an overview of production, assembly, any final product testing, and packaging of the finished medical device. Instead of

extensive documentation, a process flow chart is created and included as annex IV. The left side of the flow chart gives an overview of the process of developing STRIPA. It contains five main phases: requirements collection and selection; software design; software development and testing; software implementation and software maintenance. The right side shows detailed processes of how STRIPA is created. Sub-processes in each phase are depicted.

6. Checklist essential requirements

Medical devices for the European market have to fulfil the essential requirements specified in applicable European Directives (MDD and AIMDD). Non-CE-marked medical devices used for clinical investigations might not fulfil all essential requirements. As described above, STRIPA exactly falls into this category of research oriented non-CE-marked medical devices. Therefore, not all essential requirements are met. Annex V attaches the essential requirements list according to MDD 93/42/EEC, Annex I.

7. Risk management report

Description

The aim of hospitals is to take care of patients, by providing effective, appropriate and, in particular, safe treatments. Hospitals have to ensure the care, as adequate as possible, of patients, avoiding or at least containing damage caused by human and system errors. Therefore, a solid risk management report is required before any medical device is used within hospitals. This report intends to perform an in-depth risk assessment on the STRIPA system from various aspects so that hospitals are able to evaluate it and balance costs and benefits. A number of relevant risks are listed and described in the following table.

Intended use and identification of characteristics

The chronic use of multiple medicinal drugs is growing, partly because individual patients' drugs have not been adequately prescribed by primary care physicians. In order to reduce these polypharmacy problems, the Systematic Tool to Reduce Inappropriate Prescribing (STRIP) has been created. To facilitate physicians' use of the STRIP method, the STRIP Assistant (STRIPA) has been developed. STRIPA is a stand-alone web-based decision support system that advises physicians during the pharmacotherapeutic analysis of patients' health records [5].

The STRIP Assistant supported advice will provide clinicians with the necessary information for optimizing the individual patient's drug therapy based on a list of clinical data inputs: gender, current medical problems and diagnoses, all medicines that are actually used by the patient according to the SHIM (ATC codes) and dosage, clinical measurements such as heart rate and rhythm, blood pressure, estimated GFR (CKD-EPI formula) and other relevant laboratory data. These measurements take a few minutes, while the SHIM takes about 10 minutes. The STRIP Assistant will then generate 7 output datasets [12]:

1. correctness of drug indications by combining diagnosis/problems and medicines
2. potential prescribing omissions of beneficial drugs
3. instances of potentially inappropriate medication
4. presence of ADRs (with use of MedDRA terminology)
5. potential adverse drug interactions
6. a list of least expensive generic drugs to consider (accept/reject)
7. dosing advice

Adoption and efficacy of a decision support system might be impeded by several factors, which can be organizational, provider-related or patient related. First of all, physicians need

proper training on how to use the STRIPA, otherwise efficiency of the STRIPA could not reach a level as planned. Moreover, the STRIP Assistant is a very innovative and user-friendly software tool that is developed from a strong People-Process-Technology perspective and realizes personalization of clinical decision support software (CDSS) through unified integration architecture. By performing qualitative research in a subsample of professionals using the software, we aim to gain an in-depth understanding of STRIP Assistant users' perspectives on pharmacotherapy optimization.

Risk Matrix Used

A risk matrix (risk map) is a table (Cartesian diagram) that presents on its rows (y-axis), the category of probability (or likelihood or frequency) and on its columns (x-axis), the category of severity (or impact or consequences). Each cell of the table (or point in the Cartesian plane), which mathematically represents the product of the probability and severity values, is associated to a level of risk that eventually identifies the urgency or priority of the required mitigation actions. To measure risks identified on the STRIPA, the following risk matrix is employed. Figure 6 offers a good visualization and description of the risk matrix, where probability and severity have been split into a range of five values, whereas risk level is categorized into three classes [26].

			CONSEQUENCE				
			Minor	Moderate	Serious	Major	Catastrophic
			1	2	3	4	5
LIKLIHOOD	Rare	1					
	Unlikely	2					
	Likely	3					
	Expected	4					
	Certain	5					

Harm occurrence Likelihood levels

- Certain: will occur on every occasion
- Expected: is expected to occur in most circumstances (e.g. more than 2 times a year)
- Likely: could occur in many circumstances (e.g. probable to happen up to 2 times a year)
- Unlikely: could occur occasionally (e.g. possibility of happening once a year)
- Rare: not expected to happen, but is possible (even if no occurrence registered)

Harm severity levels

- Catastrophic: multiple deaths
- Major: possibility of death or major permanent loss of function (motor, sensory, physiologic, or intellectual)
- Serious: major injury / adverse health outcome (e.g. possibility of permanent lessening of bodily functioning)
- Moderate : moderate injury / adverse health outcome (e.g. increased length of stay)
- Minor: no or minor injury/adverse health outcome;

Estimated risk levels: –Red: unacceptable risk –Yellow: tolerable risk –Green: acceptable risk

Figure 6. Risk Matrix

Overall Risk Evaluation

In general, the overall risk evaluation of STRIPA is positive. From the risks table (shown in Annex VI), we identified some severe risks, like safety, privacy and availability, but with the mitigation measures listed in the table, these risks will be kept under control. Other less severe risks are manageable and will be minimized by their mitigation measures.

8. Product verification and validation

General

The documentation aims at providing a summary of product verification and validation documentation. The level of detail will vary significantly among different medical devices. Taken the characteristics of STRIPA into consideration, only section 8.e software is applicable.

8.a Biocompatibility

N/A

8.b Medicinal substances

N/A

8.c Biological safety

N/A

8.d Sterilisation

N/A

8.e Software

Information on the software design, the software development process and its configuration has been described in the previous sections. This section only covers tests that have been conducted. These tests include both technical tests and clinical validations that have been performed during the development. Besides, studies on usability, effectiveness and efficiency of the previous version of STRIPA provide more validation of the software [17, 18]. In addition, change and incident management of the software is also discussed in the following.

Tests

Technical tests

Automated testing of software is an essential tool in development. Unit tests are the basic building blocks for automated tests: each component, the unit, of software is accompanied by a test that can be run by a test runner over and over again without any human interaction. The software is created on frontend JavaScript and backend java. Unit tests are used on both JavaScript and java servlet. First of all, the client-side JavaScript code unit tests are performed with Unit.js which is an assertion library for JavaScript, running on Node.js and the browser. It works with many test runners or unit testing framework like Mocha, Jasmine and ect. We chose Mocha as our unit testing runner. Multiple unit tests are written on the most crucial JavaScript files, namely, strip.advice.js, strip.patient.js, strip.report.js and strip.editgui.js. Asynchronous code such as timeouts, AJAX and events are mainly tested. Moreover, a few unit tests were written to test the backend java codes. However, these java codes are not the focus of our unit tests.

Clinical validations

In collaboration with physicians from UMC Utrecht, important data inputs, including START/STOPP criteria, drug interactions and common clinical parameters, are verified. To begin with, START/STOPP criteria are manually checked and some unclear ones are discussed by a panel of experts. Medications and interactions data for the software are taken from some commercial or open databases. Developers first construct ETL processes to extract relevant data and physicians are asked to check data extracted for the software on accuracy and completeness. For inaccurate or incomplete data, new ETL processes are crafted. Through these clinical validations, data quality is very well maintained.

Usability studies on the previous version of STRIPA

To begin with, an effectiveness study was performed in an online experiment where 42 physicians were asked to use the software to perform medication reviews on two groups of polypharmacy patients. In one group, medication reviews were conducted in the usual manner, whereas the other group used the STRIPA. Changes in effectiveness were measured by comparing respondents' optimized medicine prescriptions with medication prepared by an expert panel of two geriatrician-pharmacologists. Efficiency was operationalized by recording the time the respondents took to optimize the two cases. User satisfaction was measured with the System Usability Scale (SUS). Independent and paired t tests were used for analysis. Medication optimization significantly improved with the STRIPA. Appropriate decisions increased from 58 % without the STRIPA to 76 % with it ($p < 0.0001$). Inappropriate decisions decreased from 42 % without the STRIPA to 24 % with it ($p < 0.0001$). Participants spent significantly more time optimizing medication with the STRIPA (24 min) than without it (13 min; $p < 0.0001$). They assigned it a below-average SUS score of 63.25. Therefore, we conclude that the software is proven to be effective on medication reviews for polypharmacy patients.

Another study focusing on efficiency was conducted. This study was performed in the domain of decision-supported medication reviews. Data was gathered during a randomized controlled trial. Three expert teams consisting of an independent physician and an independent pharmacist conducted 150 computerized medication reviews on patients in 13 general practices located in Amsterdam, the Netherlands. Results were analysed with a linear mixed model. A fixed effects test on the linear mixed model showed a significant difference in the time required to conduct medication reviews over time; $F(31.145) = 14.043$, $p < .001$. The average time in minutes required to conduct medication reviews up to the first quartile was $M = 20.42$ ($SD = 9.00$), while the time from the third quartile up was $M = 9.81$ ($SD = 6.13$). This leads us to conclude that the amount of time users needed to perform similar tasks decreased significantly as they gained experience over time.

Further similar tests on usability of the software will be conducted in a pilot test that starts in August 2016. This test will include more patients and physicians in comparison to previous studies.

Change and incident management

After implementing the software, there will be no new features added during the clinical trial. But changes in the database will be expected because of regular updates of drug databases in all participant countries. The federated database system described above has addressed the change management properly by storing metadata of all data that are added or removed from the system. Therefore, the system has a unique identifier for each data item so that all data become tractable through a series of updates. Besides, database updates will be performed during the period when the system is not used by any user.

Incidents or bugs of the software will be managed using GitLab.com which offers git repository management and issue tracking. A STRIPA project involving manager, developers and users has been created on the website. Users are able to report incidents as issues, then managers will assign reported issues to relevant developers and developers will fix the issues and close them. Meanwhile managers can keep track of all the incidents fixing process. The following screenshots give a brief demonstration of how these issues are reported and tracked.

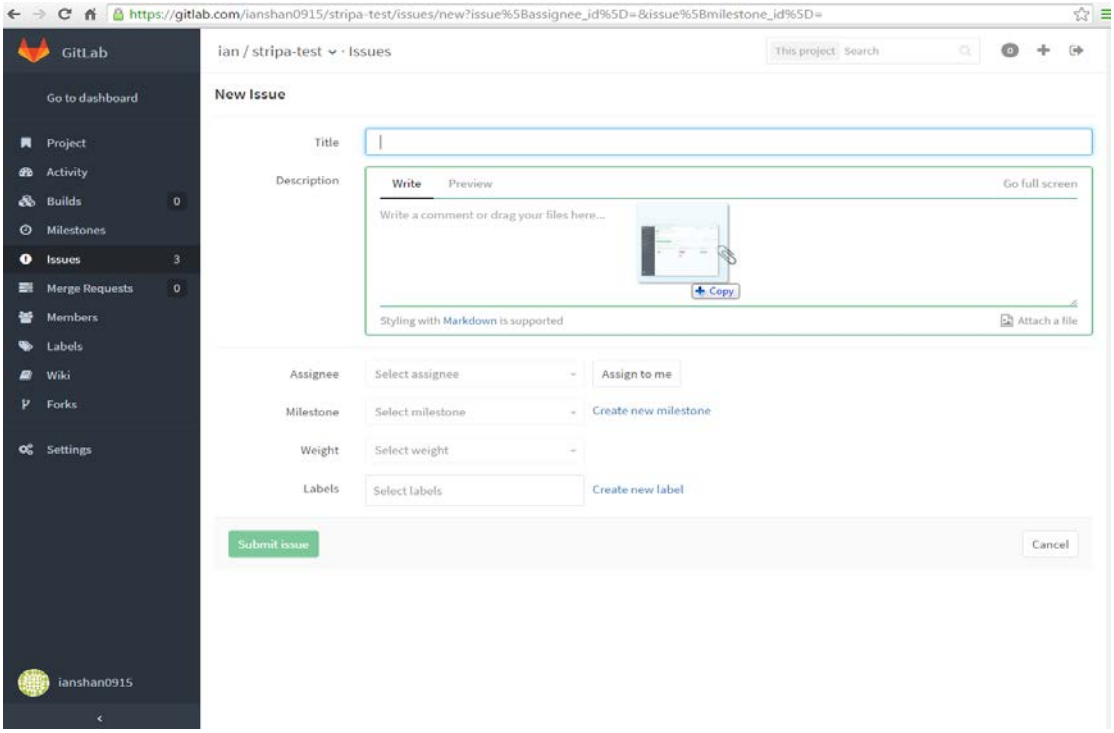

Figure 7. Reporting an incident as an issue

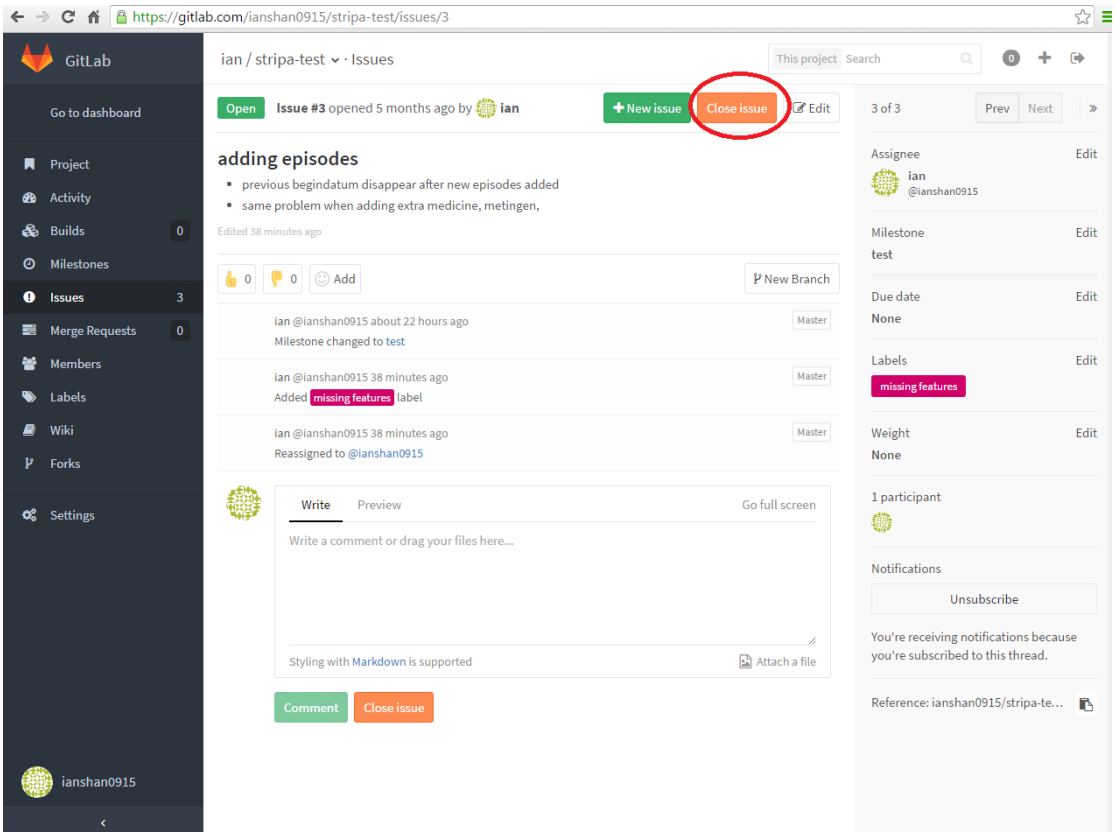

Figure 8. Closing an issue after solving the problem(s)

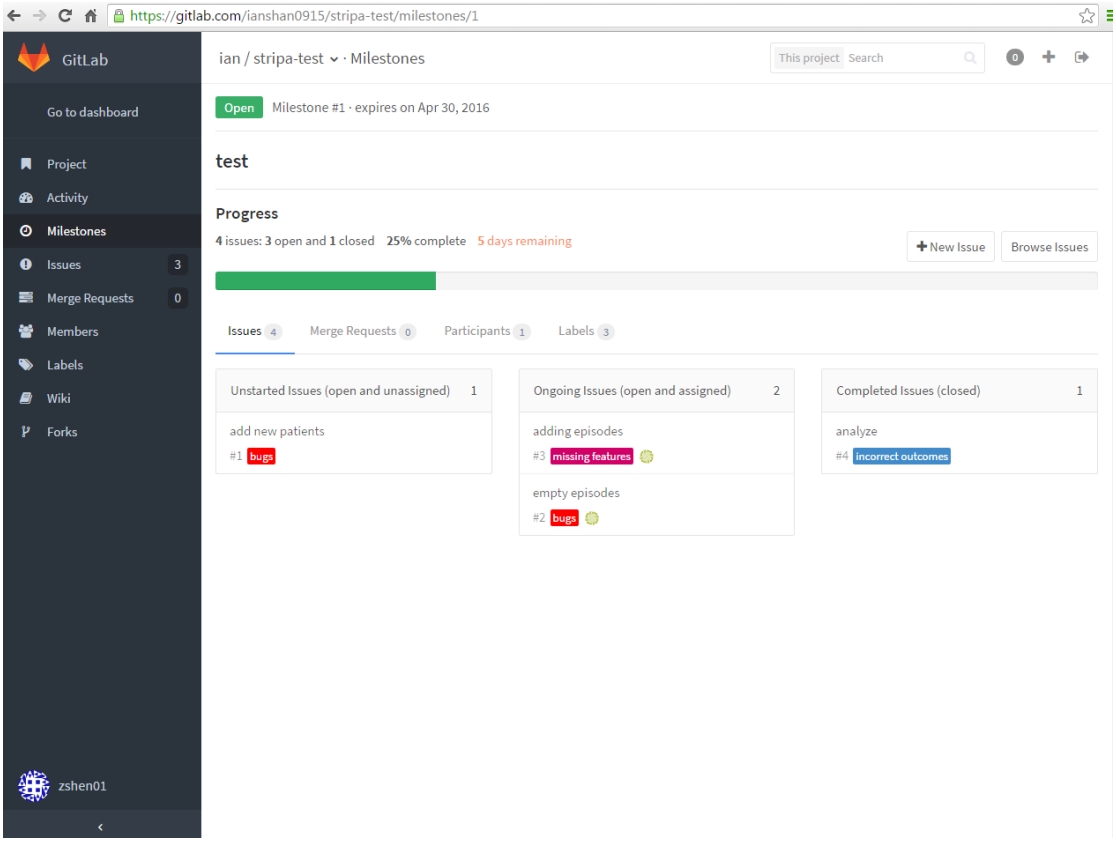

Figure 9. Milestones showing all issues and their progress

8.f Animal studies

N/A

8.g Electrical safety

N/A

8.h Clinical evidence

N/A

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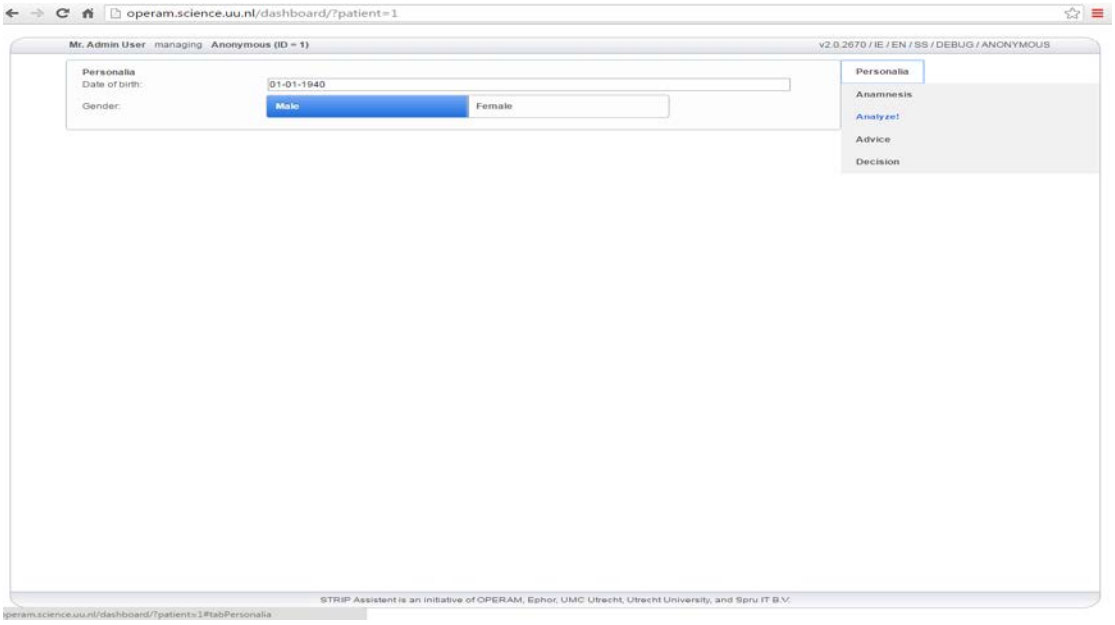
Annex I Label(s) on the device and its packaging

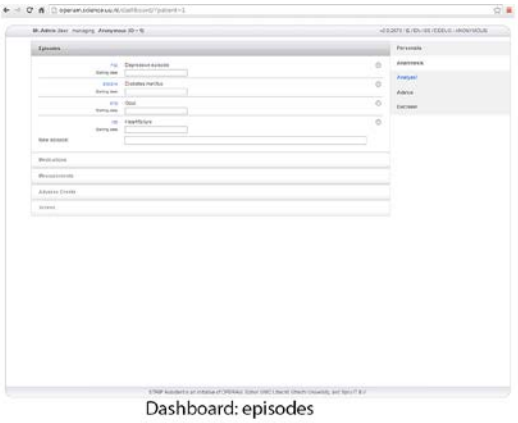
STRIPA: version 1.0

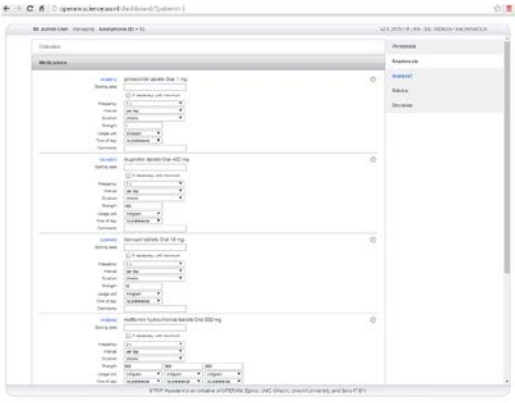
A live demonstration of the first version of the software could be found via http://videodemo.stripa.eu/english.

STRIPA: version 2.0

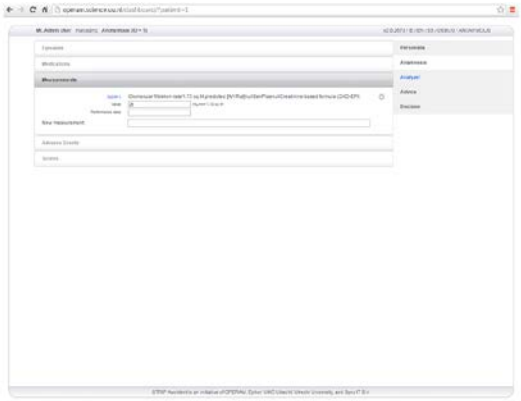


Start page showing patients basic information

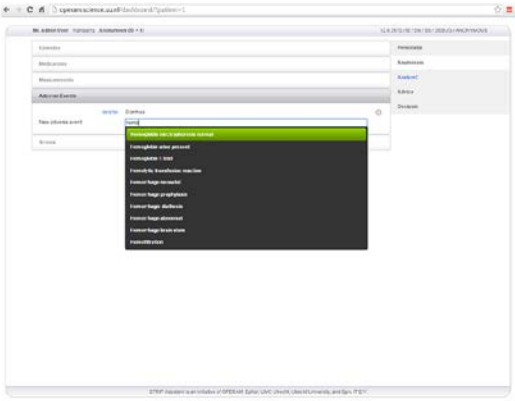

Dashboard: episodes


Dashboard: anamnesis

Dashboard where patients health records are entered

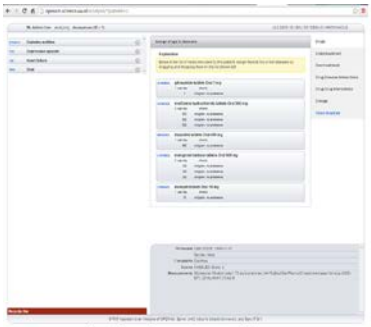


Dashboard: measurements

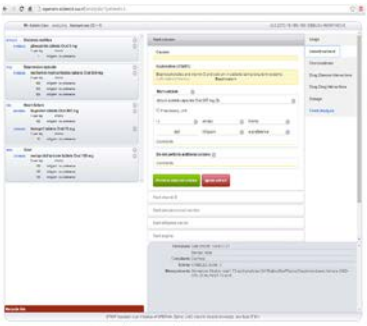


Dashboard: adding adverse events

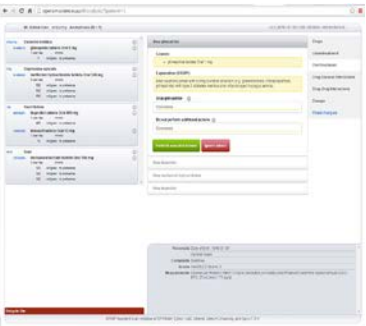
Dashboard where patients health records are entered



Analyze: drugs to prescribe

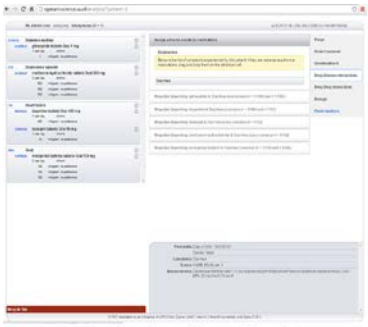


Analyze: undertreatment

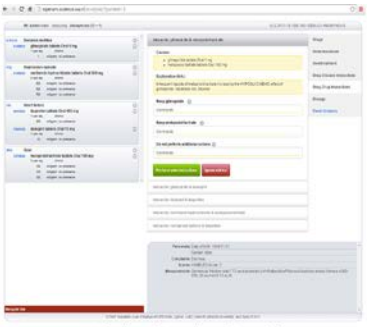


Analyze: overtreatment

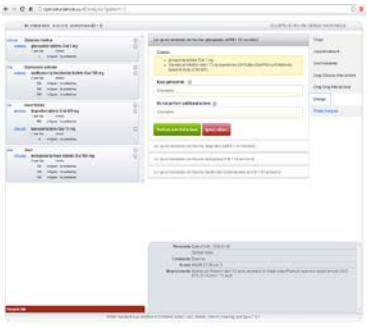
Analysis where medication reviews are conducted



Analyze: drugs disease interactions

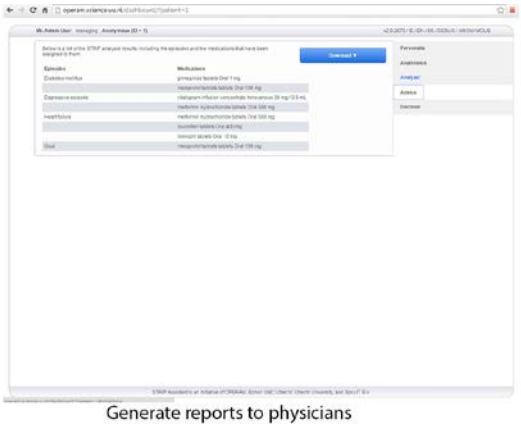


Analyze: drug drug interactions

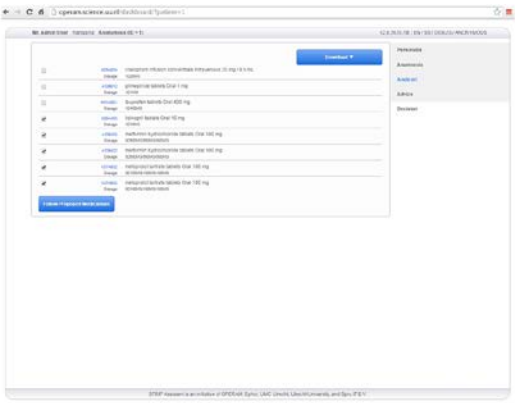


Analyze: dosage

Analysis where medication reviews are conducted



Generate reports to physicians



Generate reports to GPs

Reports are generated for both physicians and GPs after the analysis

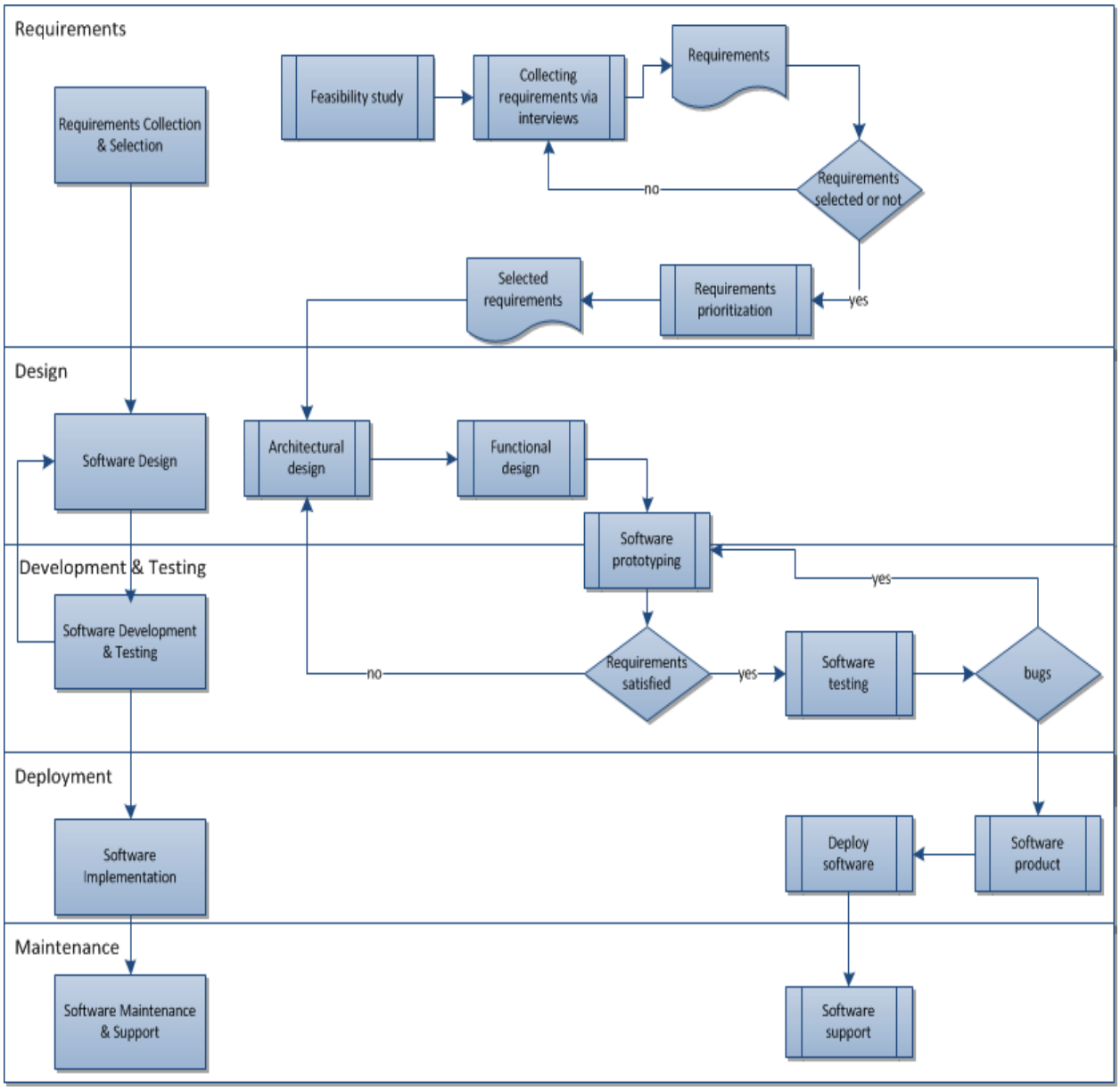
Annex II Instructions for use

A clear copy of the original instructions for use.
See 3. Instructions for use

Annex III Quality management system certificates

A clear copy of the original quality management system certificates.
N/A

Annex IV Manufacturing process



Annex V Checklist essential requirements

MANUFACTURER	
Manufacturer's Name and Address:	**Department of Information and Computing Sciences at Utrecht University** **Buys Ballot Gebouw** **Princetonplein 5,** **3584 CC Utrecht** **The Netherlands**
Product family and Medical Device(s):	**Clinical Decision Support System: STRIPA**
Classification (according to MDD Annex IX) by rule No.(s):	**Class _I__ according to rule(s) _12__**
Prepared by/signature/Date:	**Ian Shen** **05/05/2016**

Standards used to demonstrate conformity	
Document	
MDD	Medical Device Directive 93/42/EEC
Regulation (EU) No 1291/2013	Establishing Horizon 2020 - the Framework Programme for Research and Innovation (2014-2020)
CEN-EN ISO 14971:2012	Medical devices - Application of risk management to medical devices
CEN-IEC 60601-1-8:2006	Medical electrical equipment -- Part 1-8: General requirements for basic safety and essential performance -- Collateral standard: General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems
CEN-ISO 13485:2012	Medical devices - Quality management systems - Requirements for regulatory purposes
CEN-EN 62304:2006	Medical device software - Software life-cycle processes
CEN-EN 60601-1-6:2010	Medical electrical equipment - Part 1-6: General requirements for basic safety and essential performance - Collateral standard: Usability
CEN-EN 1041:2008	Information supplied by the manufacturer of medical devices

Conclusion
STRIPA is compliant with Medical Device Directive 93/42/EEC

Essential Requirements Checklist according to MDD 93/42/EEC, Annex I

Essential Requirements	Applicability (Y/N)	Reference Norm/Standard	Technical References or Procedures	Rationale for Compliance or Not (Reference ID)	Compliance (Y/N/NA)
1 The devices must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will 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 intended 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. This shall include - reducing as far as possible, the risk of use error due to the ergonomic features of the device and the environment in which the device is intended to be used (design for patient safety), and - consideration of the technical knowledge, experience, education and training, and where applicable the medical and physical conditions of intended users (design for lay, professional, disabled or other users).	**Y**	Regulation (EU) No 1291/2013 of the European Parliament and of the Council of 11 December 2013 establishing Horizon 2020 - the Framework Programme for Research and Innovation (2014-2020) Medical devices - Application of risk management to medical devices (ISO 14971:2007, Corrected version 2007-10-01) IEC 60601-1-8:2006 Medical electrical equipment -- Part 1-8: General requirements for basic safety and essential performance -- Collateral standard: General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems	Structured Tool to Reduce Inappropriate Prescribing (STRIP)	12, 16, 20,	**Y**

Essential Requirements	Applicability (Y/N)	Reference Norm/Standard	Technical References or Procedures	Rationale for Compliance or Not (Reference ID)	Compliance (Y/N/NA)
2. The solutions adopted by the manufacturer for the design and construction of the devices must conform to safety principles, taking account of the generally acknowledged state of the art. In selecting the most appropriate solutions, the manufacturer must apply the following principles in the following order: - eliminate or reduce risks as far as possible (inherently safe design and construction) - where appropriate take adequate protection measures including alarms if necessary, in relation to risks that cannot be eliminated, - inform users of the residual risks due to any shortcomings of the protection methods adopted.	**Y**	CEN-EN ISO 13485:2012 Medical devices - Quality management systems - Requirements for regulatory purposes CEN-EN 62304:2006 Medical device software - Software life-cycle processes	Structured History taking of Medication START-criteria STOPP-criteria Agile software development	6, 8, 10	**Y**

Essential Requirements	Applicability (Y/N)	Reference Norm/Standard	Technical References or Procedures	Rationale for Compliance or Not (Reference ID)	Compliance (Y/N/NA)
3. The devices must achieve the performance intended by the manufacturer and be designed, manufactured and packaged in such a way that they are suitable for one or more of the functions referred to in Article 1(2) (a) as specified by the manufacturer.	**Y**	CEN-EN ISO 13485:2012 Medical devices - Quality management systems - Requirements for regulatory purposes CEN-EN 60601-1-6:2010 Medical electrical equipment - Part 1-6: General requirements for basic safety and essential performance - Collateral standard: Usability	NAISO/IEC 25010:2011 Systems and software engineering -- Systems and software Quality Requirements and Evaluation (SQuaRE) -- System and software quality models	17, 18	**Y**
4. The characteristics and performances referred to in sections 1, 2 and 3 must not be adversely affected to such a degree that the clinical condition and safety of the patients 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.	**Y**	CEN-EN 62304:2006 Medical device software - Software life-cycle processes	NAISO/IEC 25010:2011 Systems and software engineering -- Systems and software Quality Requirements and Evaluation (SQuaRE) -- System and software quality models	17, 18	**Y**
5. The devices must be designed, manufactured and packed in such a way that their characteristics and performances during their intended use will not be adversely affected during transport and storage taking account of the instructions and information provided by the manufacturer.	**Y**	CEN-EN ISO 13485:2012 Medical devices - Quality management systems - Requirements for regulatory purposes	Web Application Deployment Guidelines	27	**Y**
6. Any undesirable side effects must constitute an acceptable risk when weighed against the performances intended.	**Y**	CEN-EN ISO 13485:2012 Medical devices - Quality management systems - Requirements for regulatory purposes		20	**Y**

Essential Requirements	Applicability (Y/N)	Reference Norm/Standard	Technical References or Procedures	Rationale for Compliance or Not (Reference ID)	Compliance (Y/N/NA)
6a. **Demonstration of conformity with the essential requirements must include a clinical evaluation in accordance with Annex X.**	**Y**	CEN-EN ISO 13485:2012 Medical devices - Quality management systems - Requirements for regulatory purposes		20	**Y**
7.1 The devices must be designed and manufactured in such a way as to guarantee the characteristics and performances referred to in Section I on the "General requirements". Particular attention must be paid to: - the choice of materials used, particularly as regards toxicity and, where appropriate flammability; - the compatibility between the materials used and biological tissues, cells and body fluids, taking account of the intended purpose of the device; **- where appropriate, the results of biophysical or modeling research whose validity has been demonstrated beforehand.**	**N**			Not applicable because no materials will be used to constructed the software product.	
7.2 The devices must be designed, manufactured and packed in such a way as to minimize the risk posed by contaminants and residues to the persons involved in the transport, storage and use of the devices and to the patients, taking account of the intended purpose of the product. Particular attention must be paid to the tissues exposed and the duration and frequency of the exposure.	**N**			As a software, the device will not be contaminated by the storage or use. Therefore , there is no risk involved in it. Whereas, as users get familiar with the software, its efficiency increases significantly.	

Essential Requirements		Applicability (Y/N)	Reference Norm/Standard	Technical References or Procedures	Rationale for Compliance or Not (Reference ID)	Compliance (Y/N/NA)
7.3	The devices must be designed and manufactured in such a way that they can be used safely with the materials, substances and gases with which they enter into contact during normal use or during routine procedures; if the devices are intended to administer medicinal products they must be designed and manufactured in such a way as to be compatible with the medicinal products concerned according to the provisions and restrictions governing those products and that their performance is maintained in accordance with the intended use.	**N**			The device does not have direct contact with any materials or medicinal products. But it runs on a PC and it generates recommendations on drug prescription, Therefore, there is no safety or compatibility issues.	

Essential Requirements		Applicability (Y/N)	Reference Norm/Standard	Technical References or Procedures	Rationale for Compliance or Not (Reference ID)	Compliance (Y/N/NA)
7.4	Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product as defined in Article 1 of Directive 2001/83/EC and which is liable to act upon the body with action ancillary to that of the device, the quality, safety and usefulness of the substance must be verified by analogy with the methods specified in Annex I of Directive 2001/83/EC. For the substances referred to in the first paragraph, the notified body shall, having verified the usefulness of the substance as part of the medical device and taking account of the intended purpose of the device, seek a scientific opinion from one of the competent authorities designated by the Member States or the European Medicines Agency (EMEA) acting particularly through its committee in accordance with Regulation (EC) No. 726/2004 (*) on the quality and safety of the substance including the clinical benefit/risk profile of the incorporation of the substance into the device. When issuing its opinion, the competent authority or the EMEA shall take into account the manufacturing process and the data related to the usefulness of the incorporation of the substance into the device as determined by the notified body. Where a device incorporates, as an integral part, a human blood derivative, the notified body shall, having verified the usefulness of the substance as part of the medical device and taking into account the purpose of the device, seek a scientific opinion from the EMEA, acting particularly through its committee, on the quality and safety of the substance including the clinical benefit/risk profile of the incorporation of the human blood derivative into the device. When issuing its opinion, the EMEA shall take into account the manufacturing process and the data related to the usefulness of incorporation of the substance into the device as determined by the notified body. Where changes are made to an ancillary substance incorporated in a device, in	**N**			Not applicable because the device does not incorporate any substance as an integral part.	

Essential Requirements	Applicability (Y/N)	Reference Norm/Standard	Technical References or Procedures	Rationale for Compliance or Not (Reference ID)	Compliance (Y/N/NA)
When the relevant medicines competent authority (i.e. the one involved in the initial consultation) has obtained information on the ancillary substance, which could have an impact on the established benefit/risk profile of the addition of the substance in the medical device, it shall provide the notified body with advice, whether this information has an impact on the established benefit/risk profile of the addition of the substance in the medical device or not. The notified body shall take the updated scientific opinion into account in reconsidering its assessment of the conformity assessment procedure.					

Essential Requirements	Applicability (Y/N)	Reference Norm/Standard	Technical References or Procedures	Rationale for Compliance or Not (Reference ID)	Compliance (Y/N/NA)
7.5 The devices must be designed and manufactured in such a way as to reduce to a minimum the risks posed by substances leaking from the device. Special attention shall be given to substances which are carcinogenic, mutagenic or toxic to reproduction, in accordance with Annex I to Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws , regulations and administrative provisions relating to the classification, packaging and labeling of dangerous substances. If parts of a device (or a device itself) intended to administer and/or remove medicines, body liquids or other substances to or from the body, or devices intended for transport or storage of such body fluids or substances, contain phthalates which are classified as carcinogenic, mutagenic or toxic to reproduction, of category 1 or 2, in accordance with Annex I of Directive 67/548/EEC, these devices must be labeled on the device itself and /or on the packaging for each unit or, where appropriate, on the sales packaging as a device containing phthalates. If the intended use of such devices includes treatment of children or treatment of pregnant or nursing women, the manufacturer must provide a specific justification for the use of these substances with regard to compliance with the essential requirements, in particular of this paragraph, within the technical documentation and, within the instructions for use, information on residual risks for these patient groups and, if applicable, 0n appropriate precautionary measures. (*) OJ 196, 16.8.1967, p 1. Directive as last amended by Directive 2006/121/EC of the European Parliament and of the Council (OJ) L 396, 30.12.2006, p. 850	**N**			Not applicable because the device does not contain any substance in the first place. Moreover, the device does not administer or remove medicines directly and it only generates recommendations with regard to adding or removing medicines.	

Essential Requirements		Applicability (Y/N)	Reference Norm/Standard	Technical References or Procedures	Rationale for Compliance or Not (Reference ID)	Compliance (Y/N/NA)
7.6	The devices must be designed and manufactured in such a way as to reduce as much as possible, risks posed by the unintentional ingress of substances into the device taking into account the device and the nature of the environment in which it is intended to be used.	**N**				
8.	**Infection and microbial contamination**	**N**			Not applicable because a software device brings no infection or contamination.	
8.1	The devices and their manufacturing processes must be designed in such a way as to eliminate or reduce as far as is possible the risk of infection to the patient, user and third parties. The design must allow easy handling and, where necessary, minimize contamination of the device by the patient or vice versa during use.					
8.2	Tissues of animal origin must originate from animals that have been subjected to veterinary controls and surveillance adapted to the intended use of the tissues. Notified Bodies shall retain information on the geographical origin of the animals. Processing, preservation, testing and handling of tissues, cells and substances of animal origin must be carried out so as to provide optimal security. In particular safety with regard to viruses and other transmissible agents must be addressed by implementation of validated methods of elimination or viral inactivation in the course of the manufacturing process.	**N**				

Essential Requirements		Applicability (Y/N)	Reference Norm/Standard	Technical References or Procedures	Rationale for Compliance or Not (Reference ID)	Compliance (Y/N/NA)
8.3	Devices delivered in a sterile state must be designed, manufactured and packed in a non-reusable pack and/or according to appropriate procedures to ensure they are sterile when placed on the market and remain sterile, under the storage and transport conditions laid down, until the protective packaging is damaged or opened.	**N**				
8.4	Devices delivered in a sterile state must have been manufactured and sterilised by an appropriate, validated method.	**N**				
8.5	Devices intended to be sterilised must be manufactured in appropriately controlled (e.g. environmental) conditions.	**N**				
8.6	Packaging systems for non-sterile devices must keep the product without deterioration in the level of cleanliness stipulated and, if the devices are to be sterilised prior to use, minimise the risk of microbial contamination. The packaging system must be suitable taking account of the method of sterilisation indicated by the manufacturer.	**N**				
8.7	The packaging and/or label of the device must distinguish between identical or similar products sold in both sterile and non-sterile condition.	**N**				
9.	**Construction and environmental properties**	**Y**	CEN-EN ISO 14971:2012 Medical devices - Application of risk management to medical devices		IMDD: Risk analysis IMDD: Instruction of Use	**Y**
9.1	If the device is intended for use in combination with other devices or equipment, the whole combination, including the connection system must be safe and must not impair the specified performance of the devices. Any restrictions on use must be indicated on the label or in the instruction for use.					

Essential Requirements		Applicability (Y/N)	Reference Norm/Standard	Technical References or Procedures	Rationale for Compliance or Not (Reference ID)	Compliance (Y/N/NA)
9.2	Devices must be designed and manufactured in such a way as to remove or minimize as far as possible: - the risk of injury, in connection with their physical features, including the volume/ pressure ratio, dimensional, and where appropriate the ergonomic features, - risks connected with reasonably foreseeable environmental conditions, such as magnetic fields, external electrical influences, electrostatic discharge, pressure, temperature or variations in pressure and acceleration, - the risks of reciprocal interference with other devices normally used in the investigations or for the treatment given, - risks arising where maintenance or calibration are not possible (as with implants) from ageing of the materials used or loss of accuracy of any measuring or control mechanism.	**Y**	CEN-EN ISO 14971:2012 Medical devices - Application of risk management to medical devices		IMDD: Risk analysis	**Y**

Essential Requirements	Applicability (Y/N)	Reference Norm/Standard	Technical References or Procedures	Rationale for Compliance or Not (Reference ID)	Compliance (Y/N/NA)
9.3 Devices must be designed and manufactured in such a way as to minimize the risks of fire or explosion during normal use and in single fault condition. Particular attention must be paid to devices whose intended use includes exposure to flammable substance, which could cause combustion.	**N**				
10. Devices with a measuring function. **10.1** Devices with a measuring function must be designed and manufactured in such a way as to provide sufficient accuracy and stability within appropriate limits of accuracy and taking account of the intended purpose of the device. The limits of accuracy must be indicated by the manufacturer.	**N**			The device has no measuring function. Therefore, this is not applicable.	
10.2 The measurement, monitoring and display scale must be designed in line with ergonomic principles, taking account of the intended purpose of the device.	**N**			The device has no measuring function. Therefore, this is not applicable.	
10.3 The measurements made by devices with a measuring function must be expressed in legal units conforming to the provisions of Council Directive 80/181/EEC, as last amended by Directive 89/617/EEC.	**N**			The device has no measuring function. Therefore, this is not applicable.	
11. Protection against radiation **11.1** General **11.1.1** Devices shall be designed and manufacturer such that exposure of patients, users and other persons to radiation shall be reduced as far as possible compatible with the intended purpose, whilst not restricting the application of appropriate specified levels for therapeutic and diagnostic purposes.	**N**			The device itself has no radiation to patients, users and other persons. Thus, there is no need to include protection against radiation in the device.	

Essential Requirements	Applicability (Y/N)	Reference Norm/Standard	Technical References or Procedures	Rationale for Compliance or Not (Reference ID)	Compliance (Y/N/NA)
11.2 Intended radiation **11.2.1** Where devices are designed to emit hazardous levels of radiation necessary for a specific medical purpose the benefit of which is considered to outweigh the risks inherent in the emission, it must be possible for the user to control the emissions. Such devices shall be designed and manufactured to ensure reproducibility and tolerance of relevant variable parameters.	**N**			The device itself has no radiation to patients, users and other persons. Thus, there is no need to include protection against radiation in the device.	
11.2.2 Where devices are intended to emit potentially hazardous, visible and/or invisible radiation, they must be fitted, where practicable, with visual displays and/or audible warnings of such emissions.	**N**			The device itself has no radiation to patients, users and other persons. Thus, there is no need to include protection against radiation in the device.	
11.3 Unintended radiation **11.3.1** Devices shall be designed and manufactured in such a way that exposure of patients, users and other persons to the emission of unintended, stray or scattered radiation must be reduced as far as possible.	**N**			The device itself has no radiation to patients, users and other persons. Thus, there is no need to include protection against radiation in the device.	
11.4 Instructions **11.4.1** The operating instructions for devices emitting radiation must give detailed information as to the nature of the emitted radiation, means of protecting the patient and the user and on ways of avoiding misuse and of eliminating the risks inherent in installation.	**N**				
11.5 Ionising radiation **11.5.1** Devices intended to emit ionising radiation must be designed and manufactured in such a way as to ensure that, where practicable, the quantity, geometry and quality of radiation emitted can be varied and controlled taking account of the intended uses.	**N**				

Essential Requirements	Applicability (Y/N)	Reference Norm/Standard	Technical References or Procedures	Rationale for Compliance or Not (Reference ID)	Compliance (Y/N/NA)
11.5.2 Devices emitting ionising radiation intended for diagnostic radiology shall be designed and manufactured in such a way, as to achieve appropriate image and/or output quality for the intended medical purpose whilst minimising radiation exposure of the patient and user.	**N**				
11.5.3 Devices emitting ionising radiation, intended for therapeutic radiology shall be designed and manufactured in such a way as to enable reliable monitoring and control of the delivered dose, the beam type and energy and where appropriate the quality of the radiation.	**N**				
12. Requirements for medical devices connected to or equipped with an energy source **12.1** Devices incorporating electronic programmable systems must be designed to ensure the repeatability, reliability and performance of these systems according to their intended use. In the event of a single fault condition (in the system) appropriate means should be adopted to eliminate or reduce as far as possible consequent risks.	**Y**	IEC 60601-1-8:2006 Medical electrical equipment -- Part 1-8: General requirements for basic safety and essential performance -- Collateral standard: General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems	NAISO/IEC 25010:2011 Systems and software engineering -- Systems and software Quality Requirements and Evaluation (SQuaRE) -- System and software quality models	17, 18 IMDD: Risk analysis	**Y**

Essential Requirements		Applicability (Y/N)	Reference Norm/Standard	Technical References or Procedures	Rationale for Compliance or Not (Reference ID)	Compliance (Y/N/NA)
12.1.a	For devices which incorporate software or which are medical software in themselves, the software must be validated according to the state of the art taking into account the principles of development lifecycle, risk management, validation and verification.	**Y**	IEC 60601-1-8:2006 Medical electrical equipment -- Part 1-8: General requirements for basic safety and essential performance -- Collateral standard: General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems	NAISO/IEC 25010:2011 Systems and software engineering -- Systems and software Quality Requirements and Evaluation (SQuaRE) -- System and software quality models	17, 18 IMDD: Risk analysis IMDD: Test	**Y**
12.2	Devices where the safety of the patients depends on an internal power supply must be equipped with a means of determining the state of the power supply.	**N**			First of all, safety of the patients are not dependent on the device at all. Secondly, the device does not require an internal power supply.	
12.3	Devices where the safety of the patients depends on an external power supply must include an alarm system to signal any power failure.	**N**				
12.4	Devices intended to monitor one or more clinical parameters of a patient must be equipped with appropriate alarm systems to alert the user of situations which could lead to death or severe deterioration of the patient's state of health.	**N**				
12.5	Devices must be designed and manufactured in such a way as to minimize the risks of creating electromagnetic fields, which could impair the operation of other devices or equipment in the usual environment.	**N**				

Essential Requirements	Applicability (Y/N)	Reference Norm/Standard	Technical References or Procedures	Rationale for Compliance or Not (Reference ID)	Compliance (Y/N/NA)
12.6 Protection against electrical risks Devices must be designed and manufactured in such a way as to avoid, as far as possible, the risk of accidental electric shocks during normal use and in single fault condition, provided that the devices are installed correctly.	**N**				
12.7 Protection against mechanical and thermal risks **12.7.1** The devices must be designed and manufactured in such a way as to protect the patient and user against mechanical risks connected with, for example, resistance, stability and moving parts.	**N**				
12.7.2 The devices must be designed and manufactured in such a way as to reduce to the lowest possible level the risks arising from vibration generation by the devices, taking account of technical progress and of the means available for limiting vibrations, particularly at source, unless the vibrations are part of the specified performance.	**N**				
12.7.3 The devices must be designed and manufactured in such a way as to reduce to the lowest possible level the risks arising from the noise emitted, taking account of technical progress and of the means available to reduce noise, particularly at source, unless the noise emitted is part of the specified performance.	**N**				
12.7.4 The terminals and connectors to the electricity, gas or hydraulic and pneumatic energy supplies which the user has to handle must be designed and constructed in such a way as to minimise all possible risks.	**N**				

Essential Requirements	Applicability (Y/N)	Reference Norm/Standard	Technical References or Procedures	Rationale for Compliance or Not (Reference ID)	Compliance (Y/N/NA)
12.7.5 Accessible parts of devices (excluding any parts or areas intended to supply heat or reach given temperatures) and their surroundings must not attain potentially dangerous temperatures under normal use.	**N**				
12.8 Protection against the risks posed to the patient by energy supplies or substances **12.8.1** Devices for supplying the patient with energy or substances must be designed and constructed in such a way that the flow rate can be set and maintained accurately enough to guarantee the safety of the patient and the user.	**N**				
12.8.2 Devices must be fitted with the means of preventing and/or indicating any inadequacies in the flow-rate, which could pose a danger. Devices must incorporate suitable means to prevent, as far as possible, the accidental release of dangerous levels of energy from an energy and/or substance source.	**N**				
12.9 The function of the controls and indicators must be clearly specified on the devices. Where a device bears instructions required for its operation or indicates operating or adjustment parameters by means of a visual system, such information must be understandable to the user and, as appropriate, the patient.	**N**				

Essential Requirements	Applicability (Y/N)	Reference Norm/Standard	Technical References or Procedures	Rationale for Compliance or Not (Reference ID)	Compliance (Y/N/NA)
13.1 Each device must be accompanied by the information needed to use it safely and **properly, taking account of the training and knowledge of the potential user, and to identify the manufacturer**. This information comprises the details on the label and the data in the Instructions for use. As far as practicable and appropriate, the information needed to use the device safely must be set out on the device itself and/or on the packaging for each unit or, where appropriate, on the sales packaging. If individual packaging of each unit is not practicable, the information must be set out in the leaflet supplied with one or more devices. Instructions for use must be included in the packaging for every device. By way of exception, no such instruction leaflet is needed for devices in Class I or Class IIa if they can be used completely safely without any such instructions.	**Y**	CEN-EN 1041:2008 Information supplied by the manufacturer of medical devices		IMDD: Instruction of use IMDD: Labels	**Y**
13.2 Where appropriate this information should take the form of symbols. Any symbol or identification colour used must conform to the harmonised standards. In areas for which no standards exist, the symbols and colours must be described in the documentation supplied with the device.	**Y**	CEN-EN 1041:2008 Information supplied by the manufacturer of medical devices	Usability Inspection Methods	IMDD: Instruction of use IMDD: Labels	**Y**
13.3(a) The label must bear the following particular: - the name or trade name and address of the manufacturer. For devices imported into the Community, in view of their distribution in the Community, the label, or the outer packaging, or the instructions for use, shall contain in addition the name and address of the authorised representative where the manufacturer does not have a registered place of business in the Community;	**Y**	CEN-EN 1041:2008 Information supplied by the manufacturer of medical devices		IMDD: Labels	**Y**

Essential Requirements	Applicability (Y/N)	Reference Norm/Standard	Technical References or Procedures	Rationale for Compliance or Not (Reference ID)	Compliance (Y/N/NA)
13.3(b) The label must bear the following particular: - the details strictly necessary to identify the device and the contents of the packaging especially for the users;	**Y**			IMDD: Labels	**Y**
13.3(c) The label must bear the following particular: - where appropriate the word "STERILE";	**N**				
13.3(d) The label must bear the following particular: - where appropriate, the batch code, preceded by the word "LOT" or the serial number.	**Y**			IMDD: Labels	**Y**
13.3(e) The label must bear the following particular: - where appropriate an indication of the date by which the device should be used, in safety, expressed as the year and month;	**N**				
13.3(f) The label must bear the following particular: - where appropriate, an indication that the device is for single use. A manufacturer's indication of single use must be consistent across the Community;	**N**				
13.3(g) The label must bear the following particular: - if the device is custom-made, the words "custom made device";	**N**				
13.3(h) The label must bear the following particular: - if the device is intended for clinical investigations, the words "exclusively for clinical investigations";	**N**				
13.3(i) The label must bear the following particular: - any special storage and/or handling conditions;	**N**				

Essential Requirements	Applicability (Y/N)	Reference Norm/Standard	Technical References or Procedures	Rationale for Compliance or Not (Reference ID)	Compliance (Y/N/NA)
13.3(j) The label must bear the following particular: - any special operating instructions;	**N**				
13.3(k) The label must bear the following particular: - any warnings and/or precautions to take;	**N**				
13.3(l) The label must bear the following particular: - year of manufacture of active devices other than those covered by e). This indication may be included in the batch or serial number;	**N**				
13.3(m) The label must bear the following particular: - where applicable, method of sterilisation.	**N**				
13.3(n) The label must bear the following particular: - in the case of a device within the meaning of Article 1(4a), an indication that the device contains a human blood derivative.	**N**				
13.4 If the intended purpose of the device is not obvious to the user, the manufacturer must clearly state it on the label and in the instruction leaflet.	**N**			The purpose is very clear.	**Y**
13.5 Wherever reasonable and practicable, the devices and detachable components must be identified, where appropriate in terms of batches, to allow all appropriate action to detect any potential risk posed by the devices and detachable components.	**N**				
13.6(a) Where appropriate, the instructions for use must contain the following particular: - the details referred to in 13.3 with the exception of d) and e);	**N**				

Essential Requirements	Applicability (Y/N)	Reference Norm/Standard	Technical References or Procedures	Rationale for Compliance or Not (Reference ID)	Compliance (Y/N/NA)
13.6(b) Where appropriate, the instructions for use must contain the following particular: - the performances referred to in section 3 and any undesirable side effects;	**N**				
13.6(c) Where appropriate, the instructions for use must contain the following particular: - if the device must be installed with or connected to other medical devices or equipment in order to operate as required for its intended purpose, sufficient details of its characteristics to identify the correct devices or equipment to use in order to obtain a safe combination;	**Y**	CEN-EN 1041:2008 Information supplied by the manufacturer of medical devices		IMDD: Instruction of Use	**Y**
13.6(d) Where appropriate, the instructions for use must contain the following particular: - all the information needed to verify whether the device is properly installed and can operate correctly and safely, plus details of the nature and frequency of the maintenance and calibration needed to ensure that the devices operate properly and safely at all times;	**Y**	CEN-EN 1041:2008 Information supplied by the manufacturer of medical devices		IMDD: Instruction of Use	**Y**
13.6(e) Where appropriate, the instructions for use must contain the following particular: - where appropriate, information to avoid certain risks in connection with implantation of the device;	**Y**	CEN-EN ISO 14971:2012 Medical devices - Application of risk management to medical devices		IMDD: Risk Analysis	**Y**
13.6(f) Where appropriate, the instructions for use must contain the following particular: - information regarding the risks of reciprocal interference posed by the presence of the device during specific investigations or treatment;	**N**				

Essential Requirements	Applicability (Y/N)	Reference Norm/Standard	Technical References or Procedures	Rationale for Compliance or Not (Reference ID)	Compliance (Y/N/NA)
13.6(g) Where appropriate, the instructions for use must contain the following particular: - the necessary instructions in the event of damage to the sterile packaging and, where appropriate, details of appropriate methods of re-sterilisation;	**N**				
13.6(h) Where appropriate, the instructions for use must contain the following particular: - if the device is reusable, information on the appropriate processes to allow reuse, including cleaning, disinfection, packaging and, where appropriate, the method of sterilisation of the device to be re-sterilised, and any restriction on the number of reuses. Where devices are supplied with the intention that they be sterilised before use, the instructions for cleaning and sterilisation must be such that, if correctly followed, the device will still comply with the requirements in section 1; If the device bears an indication that the device is for single use, information on known characteristics and technical factors known to the manufacturer that could pose a risk if the device were to be re-used. If in accordance with Section 13.1 no instructions for use are needed, the information must be made available to the user upon request;	**N**				
13.6(i) Where appropriate, the instructions for use must contain the following particular: - details of any further treatment or handling needed before the device can be used (for example, sterilisation, final assembly, etc.);	**Y**	CEN-EN 1041:2008 Information supplied by the manufacturer of medical devices		IMDD: Instruction of Use	**Y**

Essential Requirements	Applicability (Y/N)	Reference Norm/Standard	Technical References or Procedures	Rationale for Compliance or Not (Reference ID)	Compliance (Y/N/NA)
13.6(j) Where appropriate, the instructions for use must contain the following particular: - in the case of devices emitting radiation for medical purposes, details of the nature, type, intensity and distribution of this radiation.	**N**				
13.6(k) The instruction for use must also include details allowing the medical staff to brief the patient on any contra-indications and any precautions to be taken. These details should cover in particular: - precautions to be taken in the event of changes in the performance of the device;	**N**				
13.6(l) The instruction for use must also include details allowing the medical staff to brief the patient on any contra-indications and any precautions to be taken. These details should cover in particular: - precautions to be taken as regards exposure, in reasonably foreseeable environmental conditions, to magnetic fields, external electrical influences, electrostatic discharge, pressure or variations in pressure, acceleration, thermal ignition sources, etc.	**N**				
13.6(m) The instruction for use must also include details allowing the medical staff to brief the patient on any contra-indications and any precautions to be taken. These details should cover in particular: - adequate information regarding the medicinal products which the device in question is designed to administer, including any limitations in the choice of substances to be delivered;	**N**				

Essential Requirements	Applicability (Y/N)	Reference Norm/Standard	Technical References or Procedures	Rationale for Compliance or Not (Reference ID)	Compliance (Y/N/NA)
13.6(n) The instruction for use must also include details allowing the medical staff to brief the patient on any contra-indications and any precautions to be taken. These details should cover in particular: - precautions to be taken against any special unusual risks related to the disposal of the device.	**N**				
13.6(o) The instruction for use must also include details allowing the medical staff to brief the patient on any contra-indications and any precautions to be taken. These details should cover in particular: - medicinal substances incorporated into the device as an integral part in accordance with section 7.4;	**N**				
13.6(p) The instruction for use must also include details allowing the medical staff to brief the patient on any contra-indications and any precautions to be taken. These details should cover in particular: - degree of accuracy claimed for devices with a measuring function;	**N**				
13.6(q)) Date of issue or the latest revision of the instructions for use.	**Y**	CEN-EN 1041:2008 Information supplied by the manufacturer of medical devices		IMDD: Instruction of Use	**Y**

Annex VI Risk management report

The potential STRIPA hazards listed below are preceeded by an asterisk (*) if they indicate a STRIPA-specific *Device Deficiency*, i.e. “an inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling” (ISO 14155: 3.15)

Hazard	Causes	Effect of the risk	Risk Level	Mitigation measures	Actions taken when risk occurs	Risk Level	Acceptable/ not
*Encounter endless loading while conducting certain analysis	Error in the source codes, mainly situations that are not considered during the development process.	The software stops to work or parts of it do not work.	Major	Technical tests, including unit tests and black-box tests, are performed before implementing the software.	Report the problem as a new issue at gitlab.com; If urgent, contact the developer from UU for help.	Minor	Acceptable
*Encounter unexpected system failure	Unknown system bugs	The software fails to produce the expected outcomes.	Moderate	Technical tests, including unit tests and black-box tests, are performed before implementing the software.	Report the problem as a new issue at gitlab.com; If urgent, contact the developer from UU for help.	Minor	Acceptable
*Unable to access STRIPA from browsers	STRIPA web server has stopped	Users can not use the software for their medication reviews	Major	Contact UU developer team for checking web server status or fixing problems if necessary	Contact UU developer team for assistance	Minor	Acceptable
Unable to access STRIPA from browsers	No internet connection on users’ computer	Users can not use the software for their medication reviews	Major	Contact local IT support to ensure that Internet connection is available	Check Internet connection on your computer	Minor	Acceptable
Fail to get the reports	Incompatible web browser used	Final results of analysis will be not able to present to physicians and GPs.	Major	System requirements of STRIPA will be indicated explicitly in the instruction for use.	Test it with another web browser, preferably Google Chrome.	Minor	Acceptable

Missing input data	Users skip or forget some necessary input data, namely patient health records	Recommenda-tions generated by the software will not be complete or inaccurate	Moderate	List mandatory data in instruction for use, and display a warning to user when data is missing	Train all users beforehand, and display a warning to the user when data is missing	Minor	Acceptable
Encounter STRIPA UU supervision problem	Marco leaves UU for another university	Marco cannot supervise OPERAM from UU anymore	Minor	A transition procedure will be outlined	Draft transition terms with stakeholders, with Marco remaining as supervisor	Minor	Acceptable
	Marco leaves academia	Marco cannot supervise OPERAM anymore	Minor	A colleague of Marco will take his place (*e.g.* dr. Brinkhuis)	Marco will train successor	Minor	Acceptable
Encounter STRIPA UU developmen t problem	The STRIPA engineers become unavailable (accident, leave, death)	Any software problems cannot be fixed immediately	Minor	Hire replace-ments; if illness, then contact OPERAM consortium and UU	Contact hot leads individually from alumni network	Minor	Acceptable
STRIPA is struck and lost by disaster (e.g. hacked, exploded, etc)	Fire in hosting data centre, Hacked through ransom ware, other natural disasters, …	Users can not use the software for their medication reviews	Minor	Use regular backup procedures, with regular restore testing	Temporarily redirect users to Test environment: 'operam. science.uu.nl' In parallel, phone Nine support: +41 44 637 4020	Minor	Acceptable
STRIPA data are stolen and sold publicly by hackers	There is an unpatched vulnerability in one of STRIPA's libraries	Hackers gain access to the underlying databases (which contain no personally identifiable info)	Minor	Format drive, reinstall and fix the STRIPA environment from last backup; patients' privacy remains unaffected	Transparantly report on this, while technically ensuring that it cannot happen again	Minor	Acceptable

Risk management from a process perspective

In addition, please also refer to Risk management from a process perspective, for a DTAP-based software product management life cycle process view upon STRIPA's process activities and their corresponding risk control measures.

Annex VII Medicinal substances

The scientific opinion of the national competent authority or the European Medicines Agency concerns the quality and safety of the registered medicinal substance.
N/A

Annex VIII Clinical evidence

Provide data on safety and performance of the non-CE-marked device here.
N/A

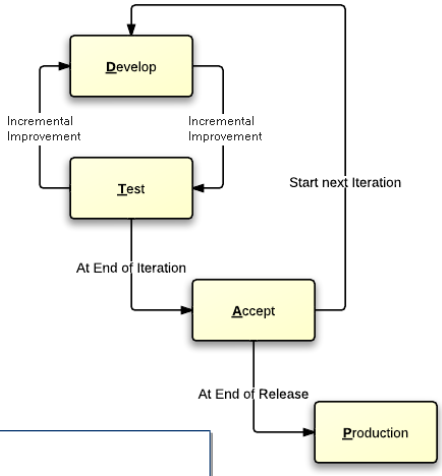
Annex IX Compliance with medical device software

A DTAP-based software product management life cycle process

To begin with, STRIPA is classified as Class A (no injury or damage to health is possible) according to the software safety classification in the norm (62304). Explanation of such a classification can be found in the device classification and the applicable classification rules of the IMDD. Therefore, not all requirements from the norm (62304) are followed. For instance, the software risk management process is simplified during the development of STRIPA, and the risk management report in IMDD offers necessary information regarding STRIPA risk management.

Secondly, annex IV shows the development process of STRIPA. The process diagram defines all the activities, tasks and their deliverables, and the software development life cycle model is incorporated in the diagram. The following table provides details on the STRIPA development process and its maintenance process by adding deliverables and risk control measures.

Finally, we implement the agile Development Testing Acceptance Production (DTAP) software life-cycle management process (see right image), extended with a separate extensive pilot phase and pre-trial two-days user software training programme.



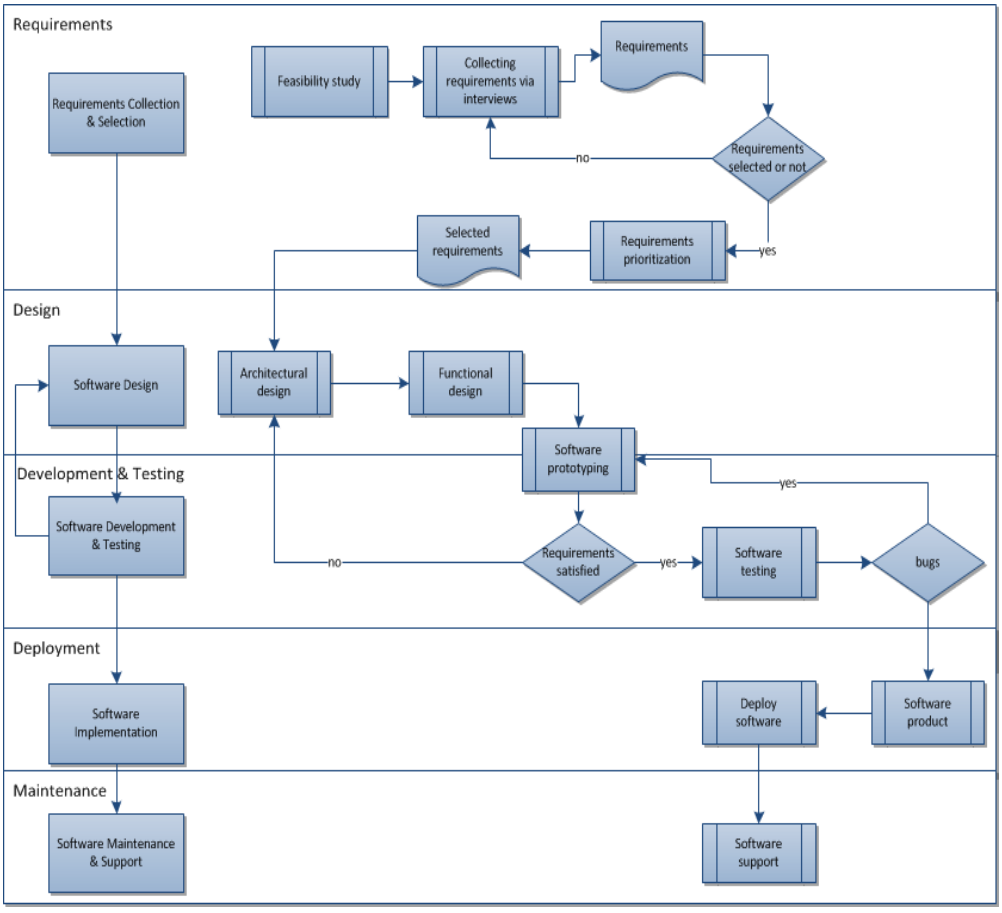


Figure 1. The STRIPA development process flow chart in IMDD annex IV used to describe the software life-cycle.

Development process activities and risk control measures

Phase	Activity	Deliverables	Deliverables description	Risk control measures (applicable)
Requirements	Feasibility study	Feasibility reports	Current status Improvements needed Physicians' attitudes Etc.	Performing multiple scientific studies
	Collect requirements	Requirements list	Purpose, when, what to do, and etc.	Involved as many GPs, pharmacists and physicians as possible
	Select requirements	Selected requirements list	Purpose, when, what to do, and selected reasons	Agile development methodology
	Requirement prioritization	Prioritized requirements list	Purpose, when, what to do, and priority	Agile development methodology
Software Design	Architectural Design	system architecture diagram	Overview of software structure, components and how they interact with each other	Peer review of software architects at ICT.OPEN/ICT.DELTA conferences
	Functional design	Software components Logical data model Data flow diagram	All functional components, Data entities and relationship, data flows	
Software Development and Testing	Prototype software	Software prototypes	Executable software or software components	Agile development methodology
	Test software	Updated requirement list, Bugs, Issues, Incident management	Updating requirement list according to the prototypes Bugs list Other problems associated with the prototypes	Gitlab.com software project management, including problems report, problems analysis, problem solving and problems tracking
		Validation process	Re-analyse the golden standard patient case set to confirm the expected advice outcomes	Expert review panel of Geriatricians & Pharmacists team consisting of Dr. W Knol MD, P Jansen MD, I Wilting MD, L Huibers MD, B Salleveldt MSc
	Build software product	Software product	Incorporate prototypes into software products	Applying the DTAP method, only after Acceptance Testing is successful, deploy software on the Production server.
Deployment	Deploy software	Deployment plan Training materials Operational software	Deployment plan describes how the software should be delivered through our	Before the deployment, a pilot test is conducted from all 4 trial sites to evaluate the usability of

			ISO 27001 certified provider Nine.ch.	the software using 40 patient cases. See pilot protocol.
			Training materials show how to use the software. A special 2-day training is organised to train all STRIPA users before the trial starts.	The production software is hosted from Nine Internet Solutions AG in Zurich, Switzerland on a flexible and scalable swiss cloud server to maximise security & privacy levels. Nine.ch is **ISO 27001 certified**.
Maintenance	Update software	Change document	Change document lists all the changes made and how often these changes happen. A list of expected risks are also provided.	Applying the DTAP method, changes are first validated at the local Development PCs, then Tested for Acceptance on the dedicated UU VM, and finally deployed on the Production servers.
	Provide technical support	Technical support or maintenance service	Email: z.shen@uu.nl m.r.spruit@uu.nl Tel: +31(30)2536454 / +31(30)2533708	UU contact persons are I Shen for technical support, and Dr M Spruit for general support.
	Sustain software	Backup procedures	Being SaaS, all software components are backuped regularly as part of the SLA.	We have selected a reputable SaaS provider with good SLA and highly responsive support desk: Nine Internet Solutions AG in Zurich, Switzerland.

Key STRIPA software reference documents

Requirements	• Meulendijk,M., Spruit,M., Drenth-van-Maanen,A., Numans,M., Brinkkemper,S., & Jansen,P. (2013). General practitioners' attitudes towards decision-supported prescribing: an analysis of the Dutch primary care sector. *Health Informatics Journal, 19*(4), 247–263. **[ISI impact factor: 0.787]** [pdf] [online] • Meulendijk,M., Drenth-van-Maanen,A., Jansen,P., Brinkkemper,S., Numans,M., & Spruit,M. (2013). Introducing the CORETEST feasibility analysis in medical informatics: a case study of a decision-supportive knowledge system in the Dutch primary care sector. In Miranda,I., Cruz-Cunha,M., & Gonçalves,P. (Eds.), *Handbook of Research on ICTs for Healthcare and Social Services: Developments and Applications* (pp. 1066–1087). IGI Global. [pdf]
Software Design	• Shen,Z., Meulendijk,M., & Spruit,M. (2016). A federated information architecture for multinational clinical trials: STRIPA revisited. *24th European Conference on Information Systems*. Istanbul, Turkey. [pdf] • Meulendijk,M., Spruit,M., Numans,M., Brinkkemper,S., & Jansen,P. (2015). STRIPA: a rule-based decision support system for medication reviews in primary care. *23rd European Conference on Information Systems* (pp. Paper 29). ECIS 2015, 26-29 May, 2015, Münster, Germany. [pdf] [online]

	• STRIPA.EU: A Federated Databases Backed Clinical Decision Support System to Support Medication Reviews in Multiple Countries (Shen). *ICT.OPEN 2016*. Intelligent Systems track. 24 March 2016, Amersfoort, Netherlands. • POMP: Polyfarmacie Optimalisatie Methode Platform (Meulendijk). ICT Delta 2011, November 16, 2011, Delft, Netherlands.
Software Development and Testing	• Meulendijk,M., Spruit,M., Drenth-van Maanen,C., Numans,M., Brinkkemper,S., Jansen,P., & Knol,W (2015). Computerized decision support improves medication review effectiveness: an experiment evaluating the STRIP Assistant's usability. *Drugs & Aging*, *32*(6), 495–503. **[ISI impact factor: 2.503]** [pdf] [online] • Meulendijk,M., Spruit,M., Willeboordse,F., Numans,M., Brinkkemper,S., Knol,W., Jansen,P., & Askari,M. (2016). Efficiency of clinical decision support systems improves with experience. *Journal of Medical Systems*, *40*(4), 1–7. **[ISI impact factor: 2.213]** [pdf] [online] • Meulendijk, M.C. (2016). *Optimizing medication reviews through decision support : prescribing a better pill to swallow*. SIKS Dissertation Series, volume 2016-02 (Dissertation). Supervisor(s): Brinkkemper, S.; Numans, M.E.; Spruit, M.R.; Jansen, P.A.F. [online] • Pilot protocol (see Annex B) • Training protocol (in prep.)
Deployment	• Standard Operation Procedure (SOP) document (see Annex A) • Trial protocol (see Annex C)
Maintenance	• DTAP life-cycle