SiMA

Simple Medicine Applicator

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EXECUTIVE SUMMARY

By the year 2050 100,000 Germans will die each year due to the rise of multi-resistant germs and the ineffectiveness of common antibiotics [1]. As a part of the Challenged Based Innovation program CBI A³ our team set out to find a solution for this societal challenge, endangering the health of the German population.

Our concept SiMA, the Simple Medicine Applicator, aims to stop the further development of multi-resistant germs, by preventing the misuse of antibiotics. Our system will achieve this by supporting users in handling antibiotics correctly, while also personalizing and optimizing antibiotic therapy.

Kristina Markl Hannah Teufel Sarah Lottner

Team Bee

We are Hannah, Sarah and Kristina, all three students of biomedical engineering, and we are part of the inno.space Design Factory at the University of Applied Sciences Mannheim. We are lucky to get the opportunity to participate in the interdisciplinary Challenged Based Innovation (CBI) program. CBI A³ is an initiative of the Design Factory Melbourne to empower students with the mindset and skills to be change makers, imagining and realizing futures that respect humans and the ecological systems we exist in. This year we are challenged with the United Nations Sustainable Development Goal 3 „Good Health and Well-Being“, connecting this with CERN technology we are looking for innovations in the future of 2030.

We are Team Bee, keen to explore the needs of the people around us, always hard working, ambitious to achieve our goal and willing to bring our ideas to the outside world.

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„THE WORLD IS HEADING TOWARDS A POST ANTIBIOTIC ERA IN WHICH COMMON INFECTIONS WILL ONCE AGAIN KILL. IF CURRENT TRENDS CONTINUE, SOPHISTICATED INTERVENTIONS, LIKE ORGAN TRANSPLANTATION, JOINT REPLACEMENTS, CANCER CHEMOTHERAPY AND CARE OF PRE-TERM INFANTS, WILL BECOME MORE DIFFICULT OR EVEN TOO DANGEROUS TO UNDERTAKE. THIS MAY EVEN BRING THE END OF MODERN MEDICINE AS WE KNOW IT."

DR. MARGARET CHAN, DIRECTOR-GENERAL OF THE WORLD HEALTH ORGANISATION FROM 2006 UNTIL 2017. [2]

SPACE PROBLEM

The correct handling of medication is a major factor for health and well-being. Unfortunately, our world is struggling with an overuse and above all with a misuse of medicine. In Germany, 30 % of the sold packages of pills are misused by the patients [3]. In case of prescription medicine like antibiotics, a misuse is causing bacteria to evolve and develop resistance to the drug and therefore has led the antibiotic to become less and less effective to treat bacterial infections.

When a new antibiotic enters the market, it often does not take long before the first resistances appear. Every use of antibiotics promotes the development of resistances: Sensitive bacteria are killed - but the resistant ones survive and continue to multiply. Antibiotic-resistant pathogens, also known as multi-resistant germs, therefore often occur where many antibiotics are used, for example in hospitals. [4]

These so-called multi-resistant germs are one of the main consequences of an incorrect handling and overuse of antibiotics. Infections with resistant pathogens are usually more difficult to treat and can take a more complicated course. People with a weak immune system, autoimmune diseases, children with immature immune defenses and elderly people, in whom the immune system is weakened, have an increased risk of such infections. Other risk groups are organ transplant patients, cancer patients undergoing chemotherapy, diabetics and patients undergoing invasive surgery. [4]

In Germany, there are around 15.000 deaths per year due to this phenomenon. According to the Robert Koch Institute (RKI), if serious underlying diseases of the patients are taken into account, it can be assumed that almost 6,000 deaths are attributed to antibiotics that have become ineffective. [5]

And if our behavior won't change soon, the development of multi-resistant germs will further increase and new diseases will be created, that cannot be treated with the existing antibiotics. In addition, harmless infections can become mortal because of the ineffectiveness of the antibiotic. As a consequence, the number of deaths every year is calculated to be around 100 000 in the year 2050 [1].

But this development did not happen without a pre-warning. Alexander Fleming, who discovered the antibiotic penicillin in 1946, already warned of such a development. He feared that the general public does not realize the real value and dangers of antibiotics and that the bacteria could evolve better defenses and resistances through reckless overuse. [2]

„THE THOUGHTLESS PERSON PLAYING WITH PENICILLIN TREATMENT IS MORALLY RESPONSIBLE FOR THE DEATH OF THE MAN WHO FINALLY SUCCUMBS TO INFECTION WITH THE PENICILLIN-RESISTANT ORGANISM. […] I HOPE THE EVIL CAN BE AVERTED. “

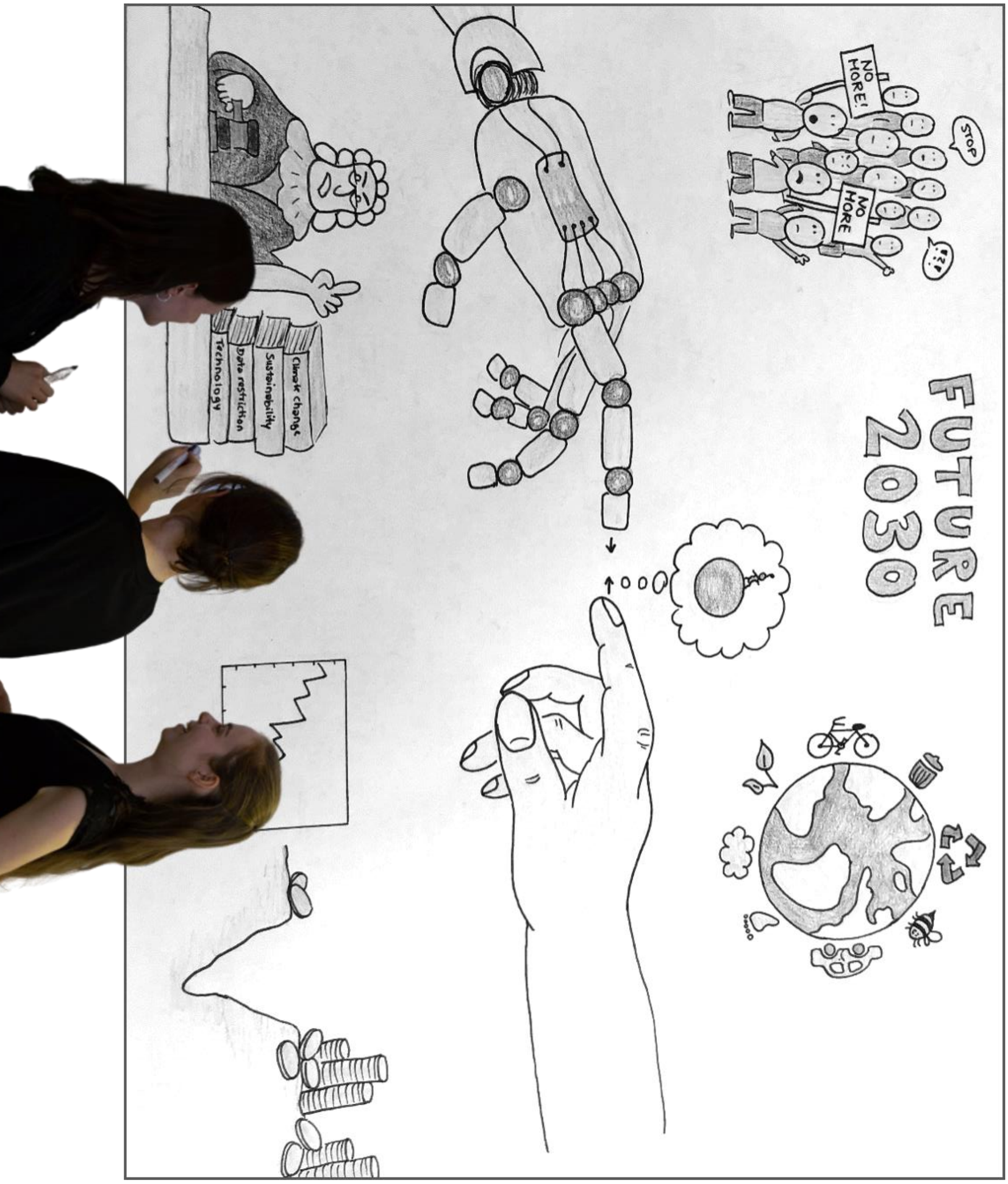
ALEXANDER FLEMING, INVENTOR OF PENICILLIN. [2]

HOW DOES THIS MISUSE OF ANTIBIOTICS LOOK LIKE?

It involves a wrong intake, where the patient does not know when or how much of the medicine he should take. Besides most patients are not aware of some incompatibilities with other medicine or food. Another misuse is an early treatment stop. Some patients just stop taking medicine when they feel better and think they are healthy again. But the fact is, that in most of these cases the germs are not completely killed and now are able to develop resistances in the body. With these left-over pills of the early finished treatment, the patient can make two mistakes. Either he flushes the medicine down the toilet, or he takes it later when he has symptoms which seem similar to the last infection.

The development of antibiotic resistance cannot be completely avoided, at best it can be slowed down. Antibiotic resistances are increasing worldwide, and they are one of the greatest challenges for global health at this time. [4]

2030



FUTURE SZENARIO

Can you imagine what the world will look like in 2030?

In order to answer this question let's take a look at current political, economic, socio cultural, technological, legal and environmental trends shaping our lives:

The last years have been mainly formed by major technological progress. Advanced technologies like Virtual Reality or Artificial Intelligence have already made it into our living room today – through gaming devices or trained algorithms for our favourite music. Additionally, we are seeing huge progress in fields like nanotechnology, microchips and transistors, making advanced technologies affordable for almost everyone.
Technological progress has also minimized the cost and effort of international trade and business. On the one hand, this interconnected world offers cultural exchange, knowledge transfer and countless business opportunities. On the other hand, it enables outsourcing to countries with fewer laws protecting workers and the environment as well as increasing traffic. At the moment we are starting to feel the consequences of climate change due to sacrificing nature for economic growth and our lifestyle.
Because of our performance and optimization-oriented society we are leading a fast-paced lifestyle which often does not leave enough time for a healthy lifestyle [6]. In addition, the rise of social media causes a decrease in personal contact and the need to achieve impossible standards set by this online world, which has a negative impact on the mental and therefore also the physical health [6]. Besides a decreasing general health, we are also experiencing a shortage of hospital and nursing staff due to low wages and challenging working conditions. This development is accelerated by an aging society [7]. Due to technological advances, people are living longer than ever before while Germany is also experiencing a demographic shift [7].
Rapid technological changes have left the political system unable to keep up with topics like digitalisation, data and IT Security. But we have also seen the political system react quickly to health threads within the past months. The focus of these regulations has been on protecting the majority of the

population, rather than respecting the wishes of individuals, like in the case of measles vaccination and COVID-19.

We believe that technological progress will continue and increase more than ever before [8]. Pushing the limits of the impossible, with leaders like Elon Musk thriving to colonize Mars.
Therefore, we suppose that in the 10 years smarter, smaller and more advanced technology will be part of the everyday life and available for almost everyone. Due to the growing demand for these products and the Asian markets ability to produce them rapidly and to affordable prizes Asian countries will be dominating the world market [8][9]. In order to compete with fast product cycles and mass production the market for personalized products will continue to grow.
This technological development will put pressure on the government to modernize regulations concerning digitalization, data and IT Security. Moreover, the people will demand more accountability and transparency in politics [8]. Furthermore, the government will continue to enforce stricter laws concerning the health and wellbeing of the population, as a reaction to the continuously decreasing general health. Lower birth rates due to an overall decline in fertility rates will add to the problem of an aging society and increase the need to solve the staff problems in the health sector [8].
In 10 years, the consequences of the environmental crisis will become more and more obvious forcing everyone to put a higher focus on environmental questions and environmentally friendly solutions [8]. In conclusion there will be more laws concerning technology, information and data security as well as sustainability to guarantee good living conditions for the next generation.
Figure 1 shows a summary of our 2030 PESTLE canvas.

Figure 1: PESTLE summary for the 2030 Future Scenario

SiMA

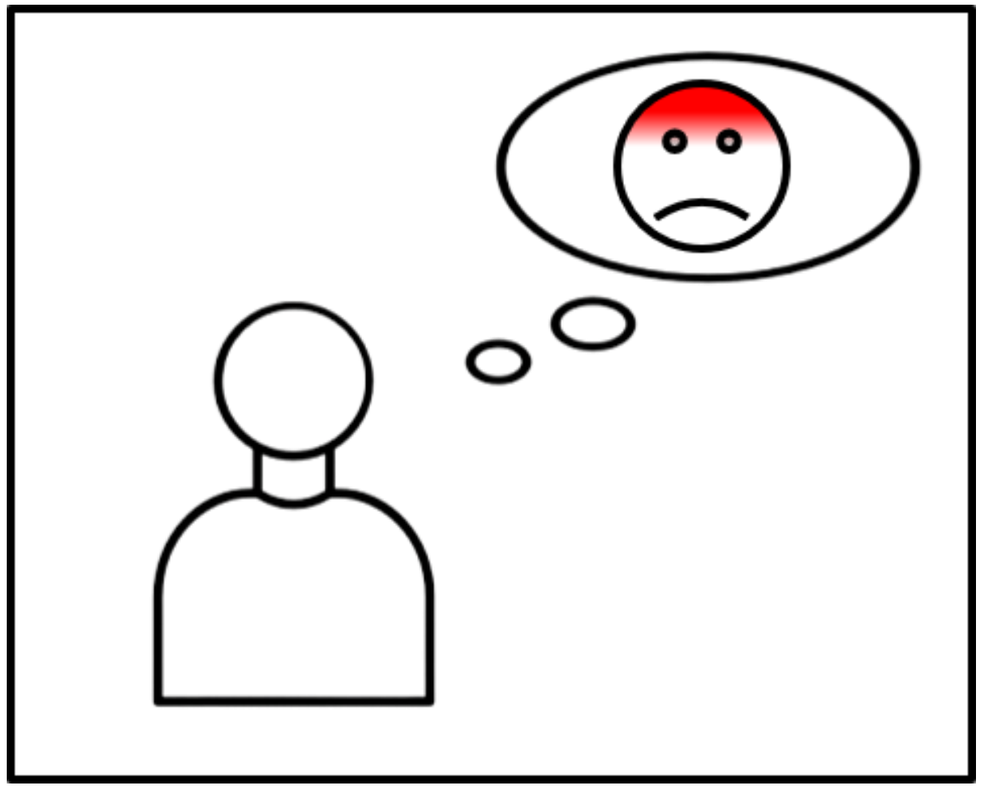
Simple Medicine Applicator

CONCEPT

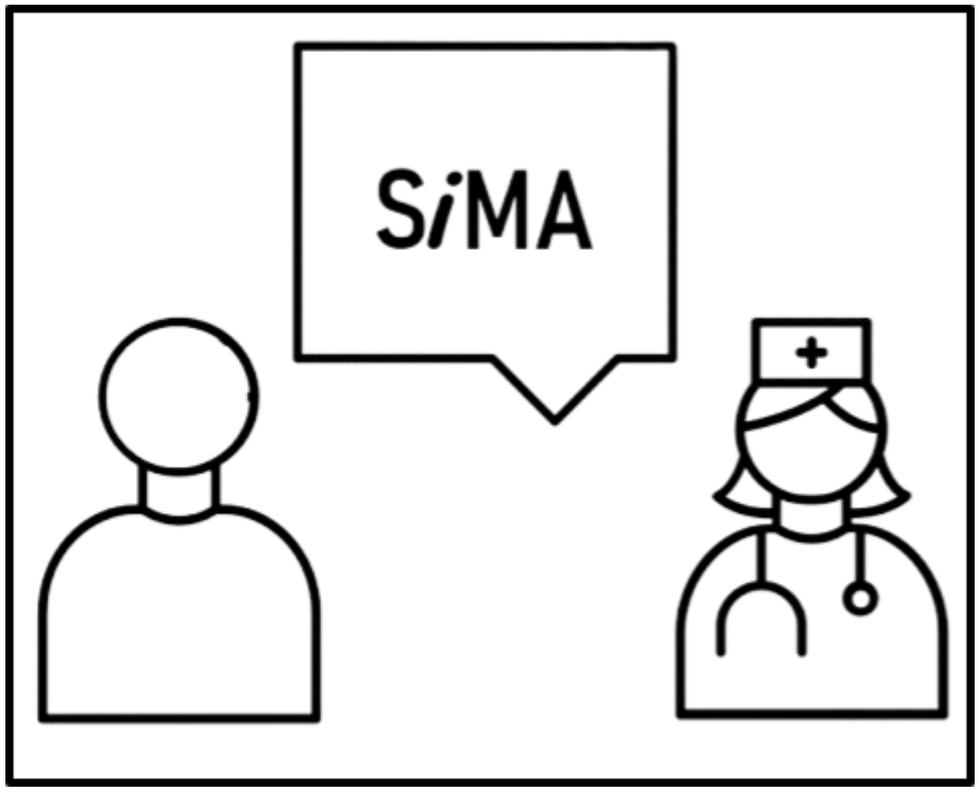
SiMA, the Simple Medicine Applicator, is our solution for a carefree and individual antibiotic therapy while leaving no space for misuse.

USER JOURNEY

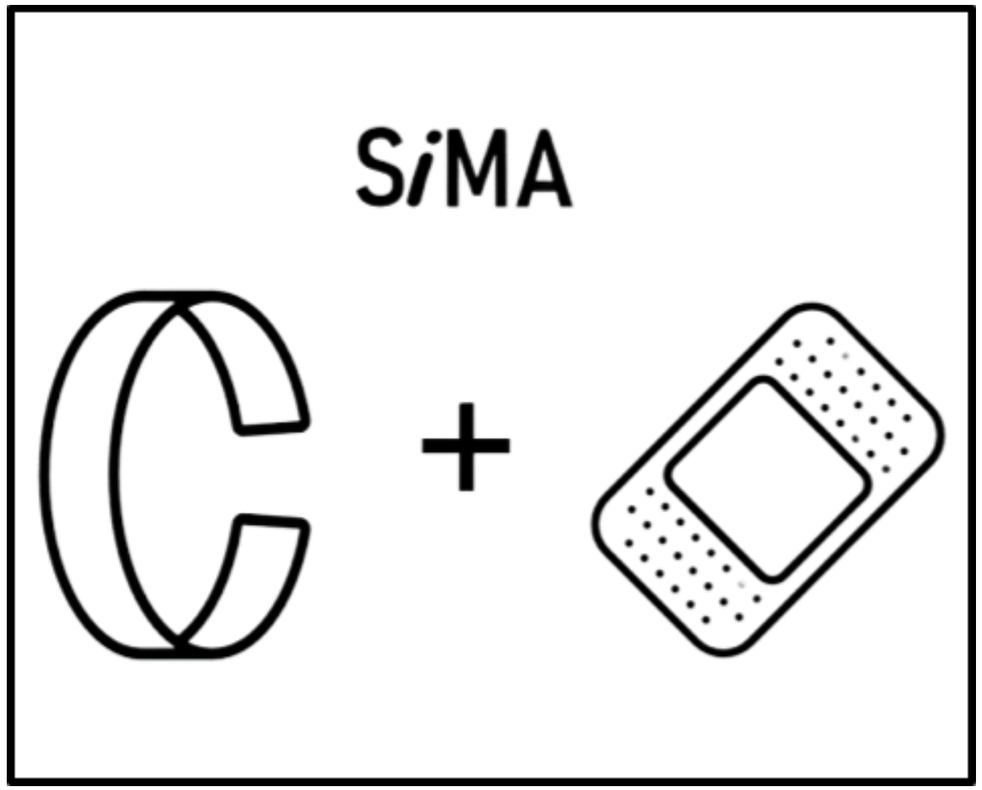
As the user is our main stakeholder for SiMA we first want to guide you through a short user journey to give an overview of the concept.



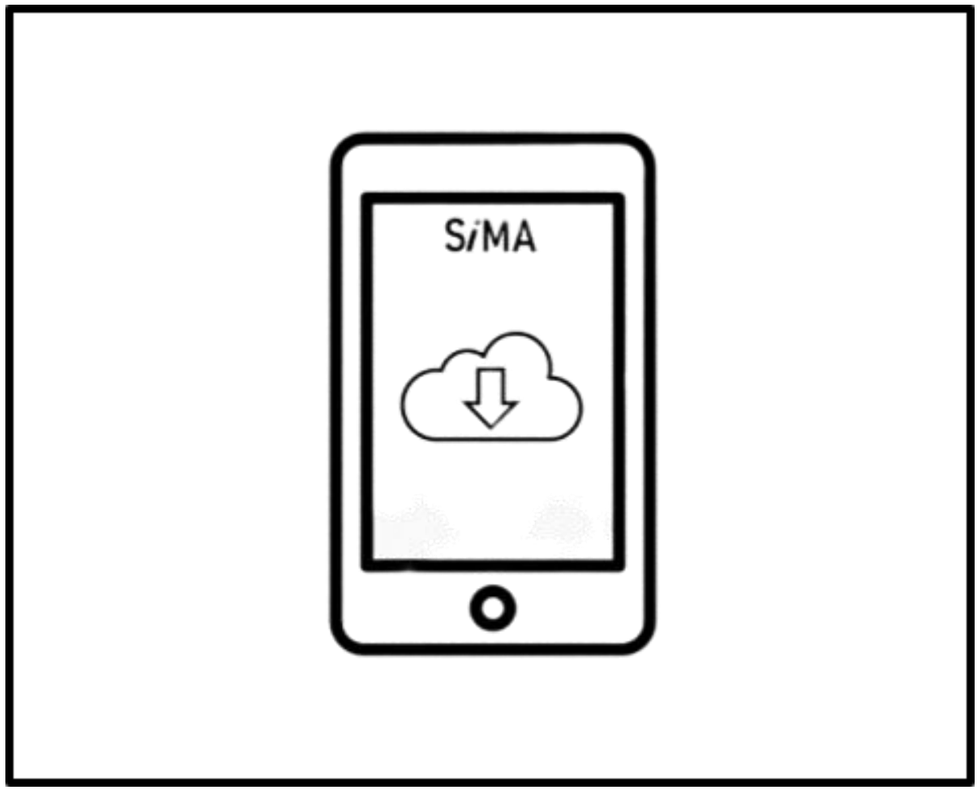
Imagine you feel sick and limp and have the feeling that you will soon get a serious infection. There is no other way than seeing the doctor.



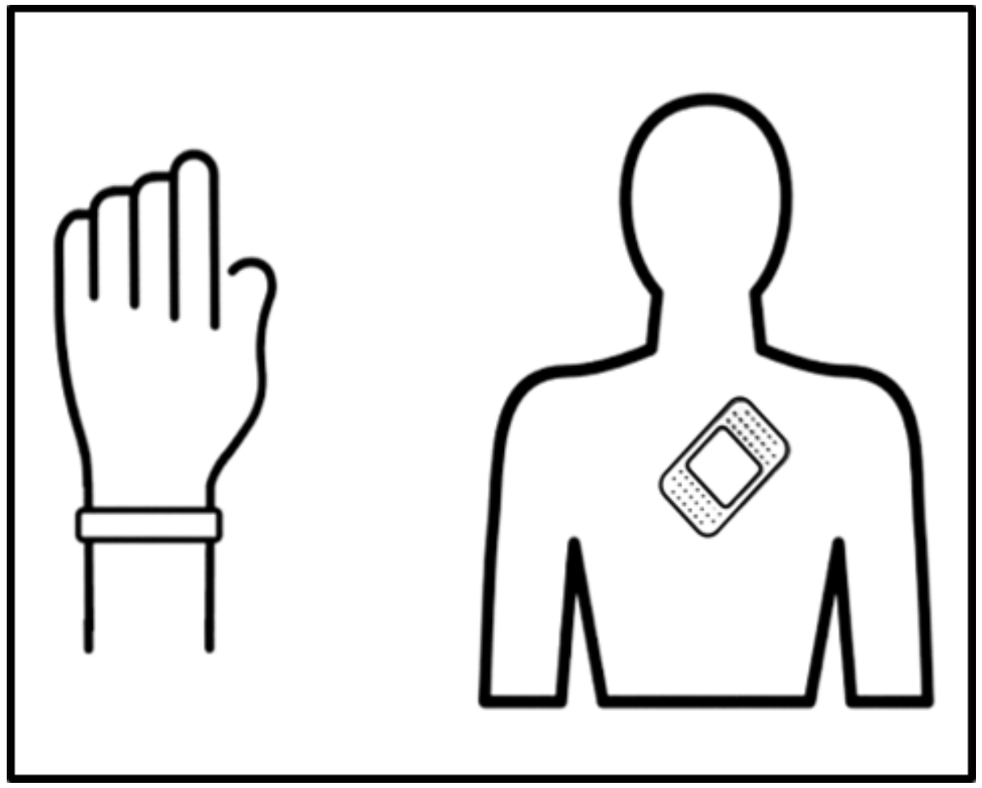
The doctor diagnoses a bacterial infection, which is usually treated with antibiotic pills. But instead the doctor prescribes the SiMA antibiotic therapy. SiMA, the so-called Simple Medicine Applicator, makes every antibiotic treatment easy and efficient by giving the antibiotic through your skin, so that you no longer have to worry about taking pills.



SiMA comes up with a sensor bracelet and transdermal patch. The sensor bracelet tracks your health state and the metabolization of the medicine continuously during the whole treatment. This information will be used to control the dose and the application intervals of the transdermal patch to ensure an optimal therapy.

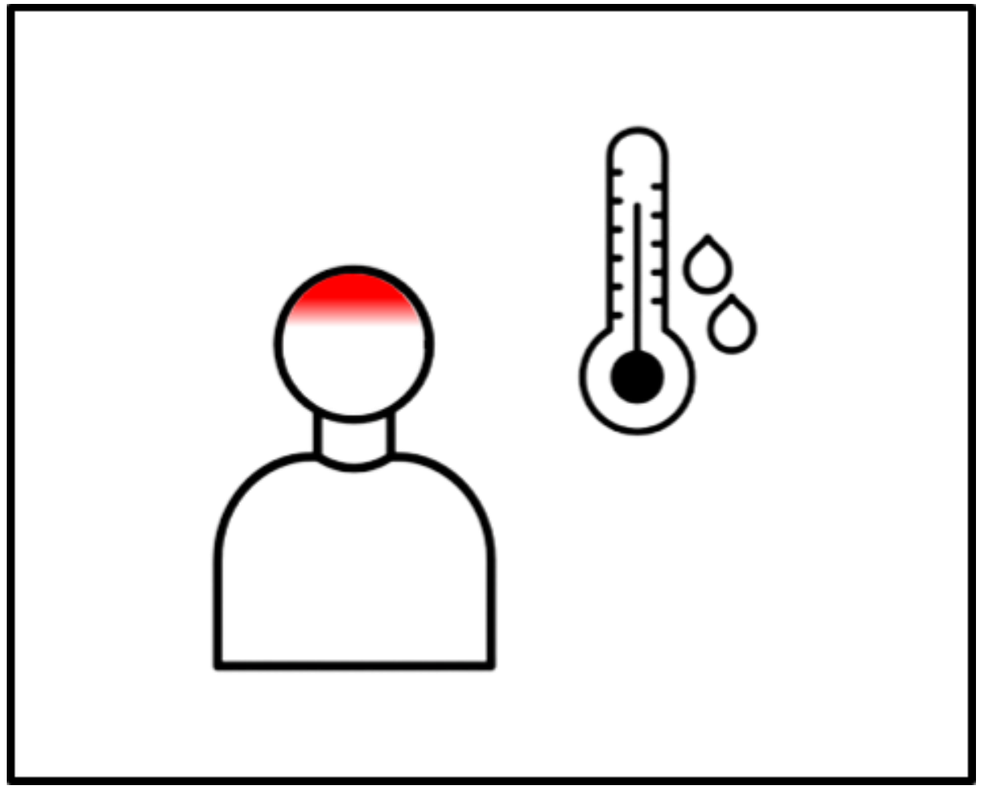


After getting the recipe and picking SiMA up at the local pharmacy, as you would do it with normal medicine, you download the SiMA App to set up the bracelet and the patch. The App will give you detailed instructions on how to use it and more information about your therapy as well. This moreover includes that you will be shown the right application spot on your body, as the skin thickness of the different body areas also plays a role in optimal transdermal absorption.



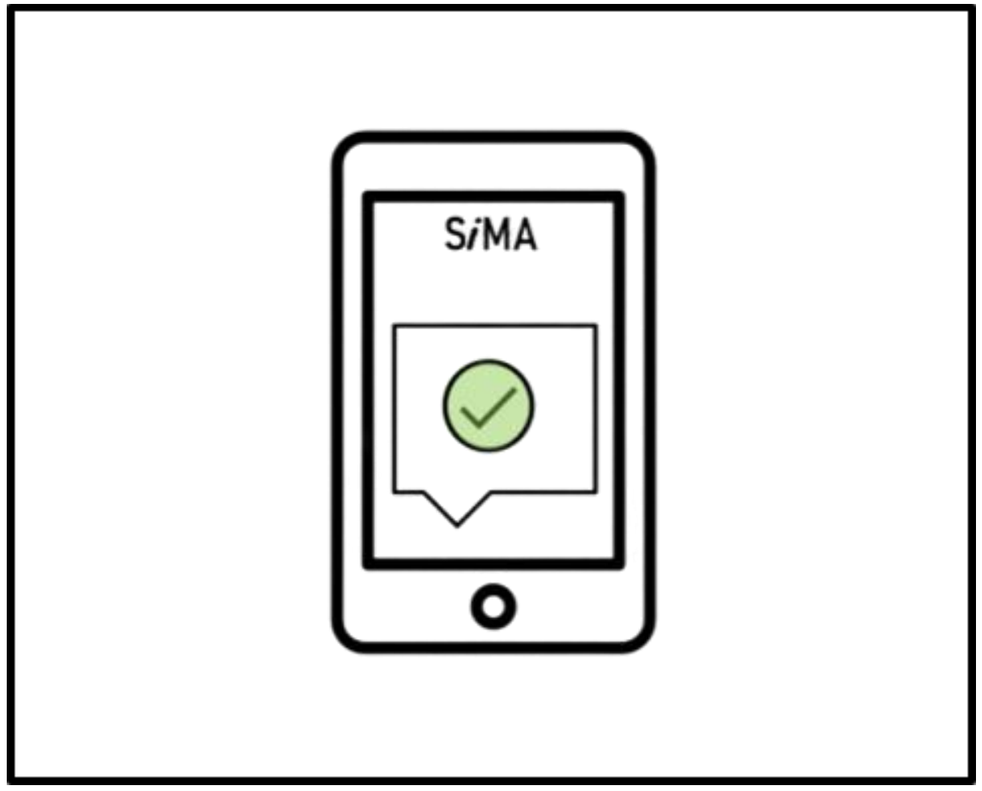
All you have to do now is put on the bracelet and place the patch on your body. As soon as the patch recognizes skin contact it will be activated and the treatment will start.

Besides, the doctor will be notified and can monitor your health state and vital parameters at the SiMA Desktop Application during the whole treatment. Together with the doctor, the SiMA System takes care of your therapy, which is why you do not have to think about taking the right amount of medicine at the right time. The dose will be adjusted automatically due to your current health state by the trained intelligent SiMA System.

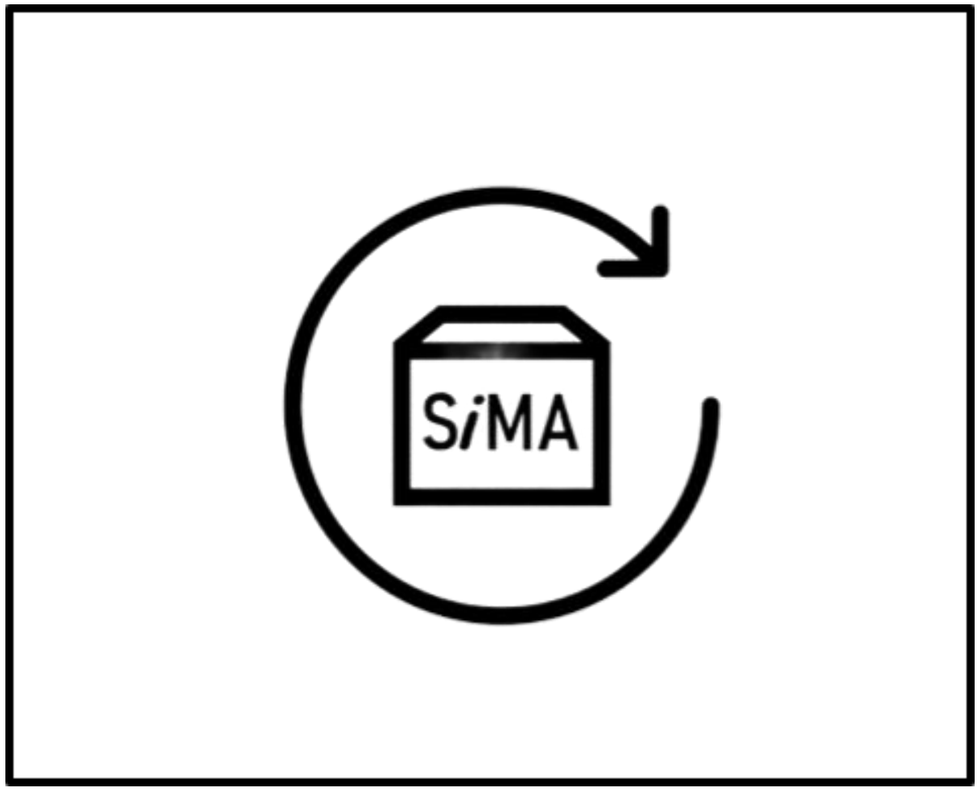


During every treatment it is also possible that side effects such as high fever, high or low blood pressure or nausea occur, because every body responds different to the medicine. In this case, SiMA identifies the critical situation and acts accordingly in changing the dosage.

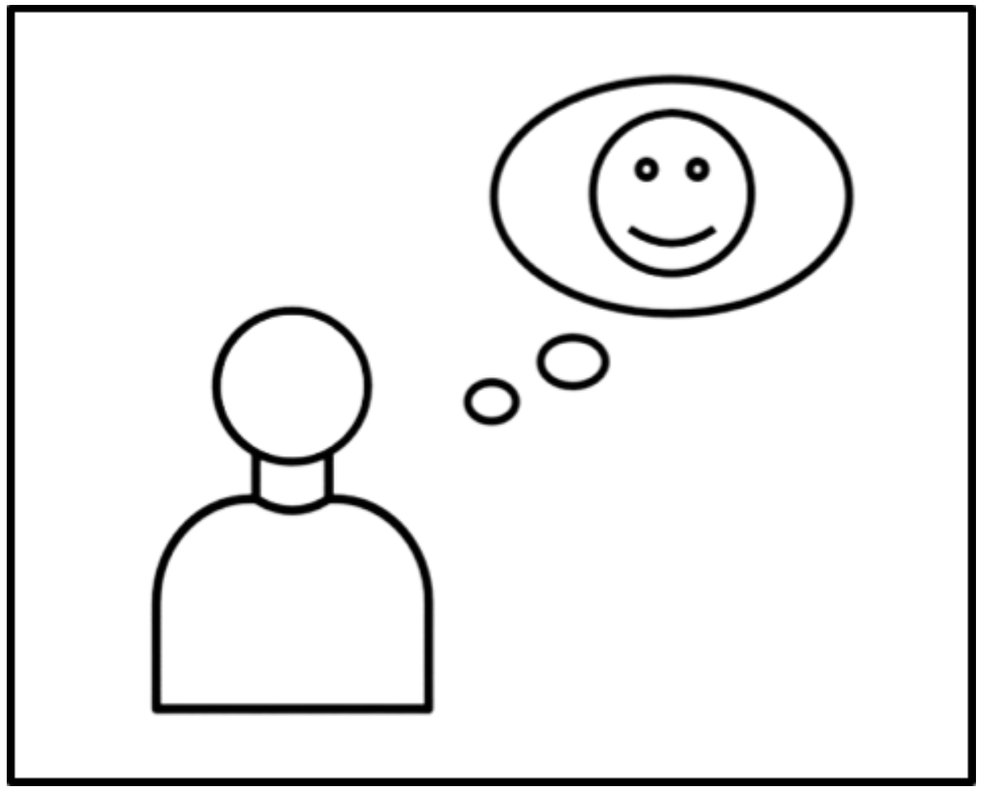
Nevertheless, the doctor will be alerted to double check the dose and is also able to adjust it manually.



Via the SiMA App you stay informed about all the actions and the therapy course as well. You will also get a message if the treatment is finished and the patch stops giving medicine before you can remove the patch and take off the bracelet.



As a final step of the SiMA antibiotic therapy, you return the components to your local pharmacy, so that they can be prepared for sterilization and reused for the next patient. Additionally, the SiMA system is sustainable as less waste is produced and the incorrect disposal of any remaining antibiotic is avoided.



In the end you will profit of a stress-free recovery which pleases not only you, but also the whole society and the environment

SENSOR BRACELET

Our first component is the sensor bracelet. It is used to measure all the parameters that are needed for the automated dosage adjustments. This will include measuring the vital functions of the patient as well as the antibiotic metabolization.

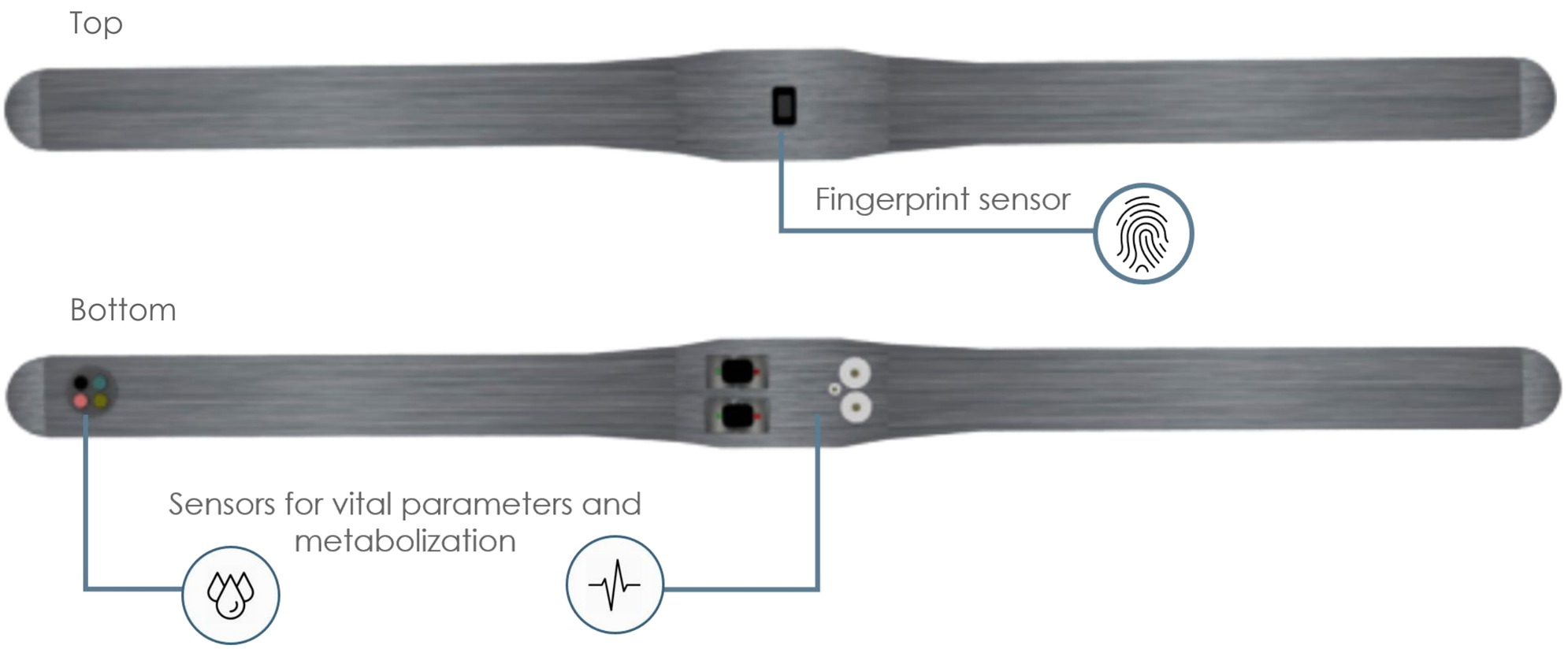


Figure 2: Top and bottom view of the SiMA bracelet

As you can see in the figure above, the SiMA bracelet looks similar to fitness trackers already on the market and the user can choose from different styles and materials. Due to this, the patient does not have to worry about being stigmatized because of his therapy but can wear the SiMA bracelet out in public without anyone noticing he is having an antibiotic therapy. The whole bracelet is waterproof and super elastic so that it can really be worn the whole day without the need or desire to take it off. Additionally, the bracelet is equipped with a fingerprint sensor. If the bracelet has to be removed for a specific reason, the user must first can his fingerprint when putting it back on. This ensures that each user only ever wears the bracelet selected for his therapy and prevents the bracelets from being accidentally mixed up. It also helps avoiding possible misuse by unauthorized persons. The bracelet is featured with a quick-charging function, so you only need to plug it in for about 30 minutes to charge it. Fully charged, the bracelet will stay functioning for 2 to 3 days. This ensures that it only has to be taken off for a period as short as possible. To be able to read out the fingerprint and to communicate with the data management tool there is a microchip integrated into the bracelet.

VITAL PARAMETER SENSING

But let us now have a closer look at the heart of the bracelet: the vital data tracking by biosensors. These sensors are needed to always be able to check the current health status of the patient and to ensure that the therapy is really functioning. The data will be continuously sent to the data management tool, where it will be analyzed to be used for personalizing the therapy. To do this, we will include the following five sensors seen and described below, for vital data tracking. All of these are located at the top of the wrist of the patient.

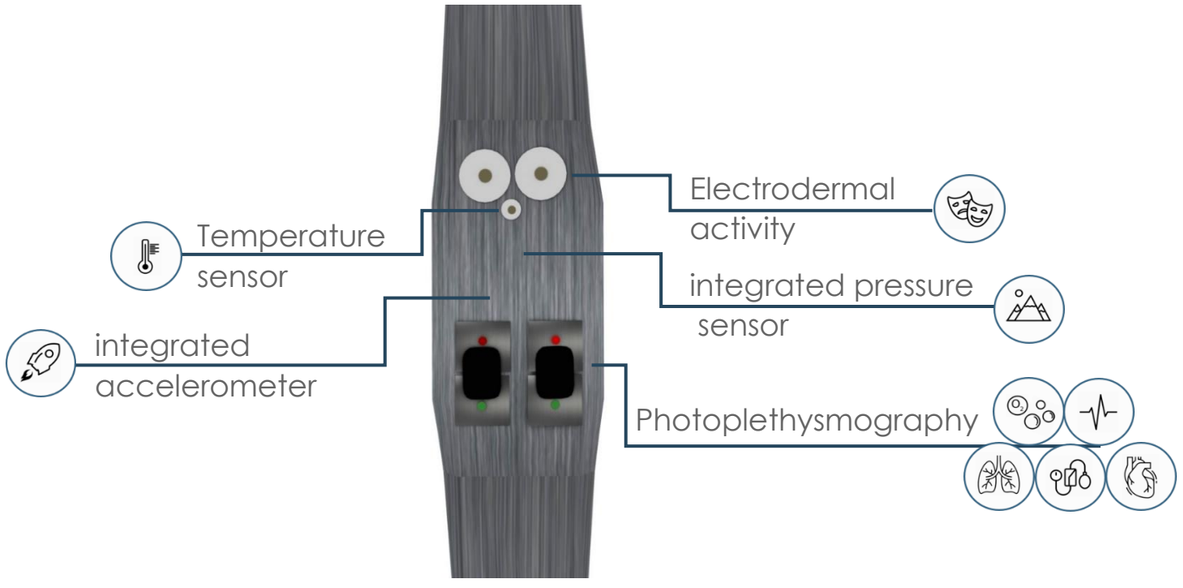


Figure 3: Vital parameter sensors of the SiMA bracelet

PHOTOPLETHYSMOGRAPHY

Photoplethysmography (PPG) is a non-invasive optimal measurement method to detect vital function that are related to the blood and its flow. PPG uses a light source and a photodiode to detect differences in the reflected light of a surface or tissue. For the measurement of blood parameters, the light source and the photodiode are placed at the top of the skin and the light will pass through the skin until it reaches the blood vessels where it is reflected. The photodiode then will capture the reflected light. Since the blood volume changes during one heart pumping interval, more or less photons will be reflected by the blood which makes it possible the determine blood related vital parameters by analyzing the reflected light. In the case of SiMA a green LED is used as the light source. Due to its relatively small wavelength of around 500nm the penetration depth is slightly short which keeps the background noise at a low level. This will make the measurement more accurate compared to other light sources. A graphic of the measurement principle can be seen below. [10] [11]

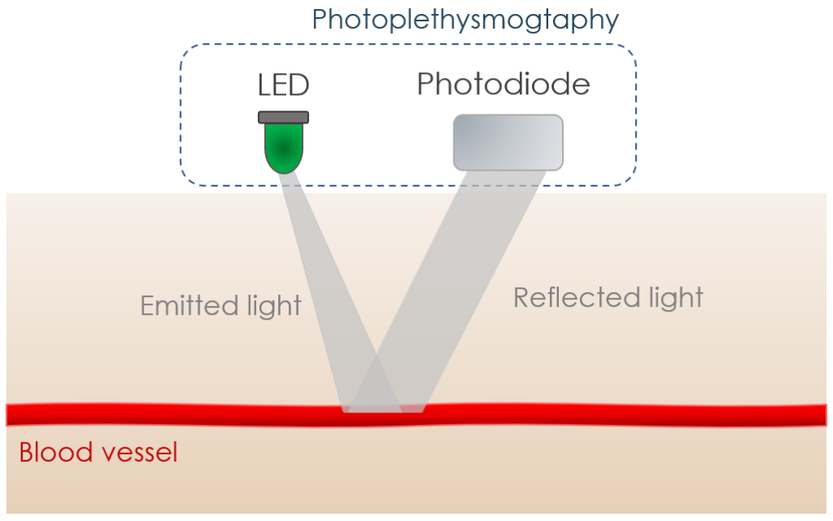


Figure 4: Functional principle of photoplethysmography

The PPG will enable us to capture a beat-to-beat analysis of the blood flow which is also known as the heat-rate variability. This is done by measuring the time difference of two consecutive signal maxima captured by the photodiodes. By averaging this beat-to-beat analysis we will moreover be able to detect the pulse rate.

In combination with the signals of the accelerometer, which is measuring body movement, the beat-to-beat signal of the blood can moreover be used to calculate the breathing rate of the patient, which is done by tracking the respiratory peak within the beat-to-beat signal. Looking at the state of art this is currently only possible while sleeping since the artefact due to body movements are too high during the day. But we belief that until SIMA will enter the market it is possible to deduct all movement artefacts by analyzing movement patterns captured by the accelerometer. [12]

The analysis of the breathing frequency is especially necessary if the bacterial infection is located at the cervical or throat region for example if the patient is suffering from a lung infection, since this can strongly influence his breathing [13]. Moreover, heavy and irregular breathing can be symptoms of exhaustion.

To be able to detect the blood pressure the bracelet will include two sets of photoplethysmography, which are placed at a dedicated distance from each other along the blood vessel. To estimate the blood pressure the so-called pulse transit time (PTT) is used. The PPT is determined as the time that the impulse caused by the contracting heart takes to get

from one point to another. This can be measured by capturing the time that it takes for the signal maximum received by the first photodiode to reach the second. Looking at current smart watches and fitness trackers, the blood pressure is a parameter, that is normally not integrated. The reason is, that it is necessary to compromise the arm using a cuff in order to measure the blood pressure while using sensors only placed on the arm. A cuff is nothing that can be implemented into a bracelet and it is even not even suitable for continuous measurements over a longer interval. In order to assess blood pressure without cuffs, it is necessary to measure it on extremities like the finger. For this method an additional sensor, to the one in the bracelet, is needed, which is not practical for continuous use as well. But research is already making great progress within this field so we are convinced that by the year 2030 the blood pressure can be estimated only using two PPG signals captured within the bracelet. [14][15][16]

The only blood parameter that cannot be measured with the green LED is blood oxygen. This is due to the fact, that hemoglobin is not reflecting green light very well but only red and infrared light. Moreover, hemoglobin has different optical characteristic, so that it reflects different amounts of light whether it is bound with oxygen or not. In addition, oxygenated and deoxygenated hemoglobin have different reflection characteristics, so that they will react differently while being exposed to red and the infrared LED. To measure the oxygen saturation of the blood we use one red and one infrared LED together with another photodiode. By capturing the light reflected by the hemoglobin while being stimulated with the LED light and analyzing the signal later, it is possible to determine blood oxygen saturation of the patient. [16]

ACCELEROMETER

Working closely together with the photoplethysmography is the accelerometer. It is measuring the patient's acceleration relatively to the acceleration of gravity. By analyzing this data, it is possible to determine movement and gait of the patient. Within SiMA a capacitive accelerometer will be used that can measure acceleration for all three dimensions, which makes the measurement most accurate. [17]

The data from the accelerometer is on the one hand used to remove motion artefacts from the PPG signal. Moreover, the activity and gait of the patient during the day can be monitored. The physical activity of the patient is an indicator for an improved health condition since people normally rest more when they feel sick. Additionally, gait anomalies can be tracked that can for example be triggered by dizziness or loss of balance. This could on the one hand be symptoms of the sickness on the other hand this could be a possible side-effect of the medication therapy. While the patient is asleep, the accelerometer data can additionally be used to track the patient's sleep quality. All this data will not only be used to monitor the recovery of the patient but can moreover be used to give the patient suggestions for behavioral changes in case he is not resting enough to recover most effectively.

TEMPERATURE SENSOR

For measuring the patient's body temperature, we will use a polymeric thermistor. A thermally sensitive resistor is an electrical resistor that will change its resistance due to temperature. By applying the sensor to the skin, the resistance of the thermistor can be measured, and the temperature can be calculated. In fact, the sensor does not directly measure body temperature but skin temperature. Nevertheless, body temperature can be easily determined from the measured values.

Compared to the temperature sensors available nowadays, SiMA will use an optimized sensor that is less affected by environment temperature and the patient's sweat to make our measurements most reliable. By monitoring the patient's body temperature, we will be able to track the health status of the patient precisely, since rising temperature or fever are common indicators for viral as well as bacterial infection. In case the temperature is falling during the therapy its effectiveness can be checked, in contrast continued fever can be an indicator of a non-suitable therapy or too low medication dosage, which then can be easily adjusted. [16][18]

PRESSURE SENSOR

Our integrated, barometric pressure sensor will on the one hand help us to detect the altitude the patient is living in. With this we want to find connections between altitude and therapy effectiveness of the medication. On the other hand, the pressure sensor will allow us to detect sound vibrations of the environment. The analysis of this vibrations will enable us to determine the level of noise in the patient's environment. To rest and recover as effective as possible the patient needs a peaceful and preferably quite surrounding to lower his stress level and fully concentrate on recovery. If this is not given, the recovery can take longer than expected. In this case, the SiMA App will give the patient suggestions in how to change his environment to improve his therapy success. [16]

ELECTRODERMAL ACTIVITY

The sensor for electrodermal activity (EDA) will enable us to not only measure the physical condition of the patient but also his mental health. An EDA sensor measures skin conductivity by using two small electrodes and applying a short current in between. The sensor will measure different currents due to the change of skin resistance. A schematic of the measurement principle can be seen in figure 5. These changes are caused by the different activities of the parasympathetic and sympathetic nerves. While the parasympathicus is more active when a human is relaxed the sympathetic nerves are more involved if people are physically active or nervous [s10]. Moreover, stress and activity will lead to an increased sweat production, which also has effects on the skin resistance. By analyzing this EDA data, we can monitor the metal condition of the patient during therapy. This is a good indicator for therapy success since the patient will be less stressed when feeling better but can also help by detecting side effects if the stress level rises unnaturally during the treatment. [16][20]

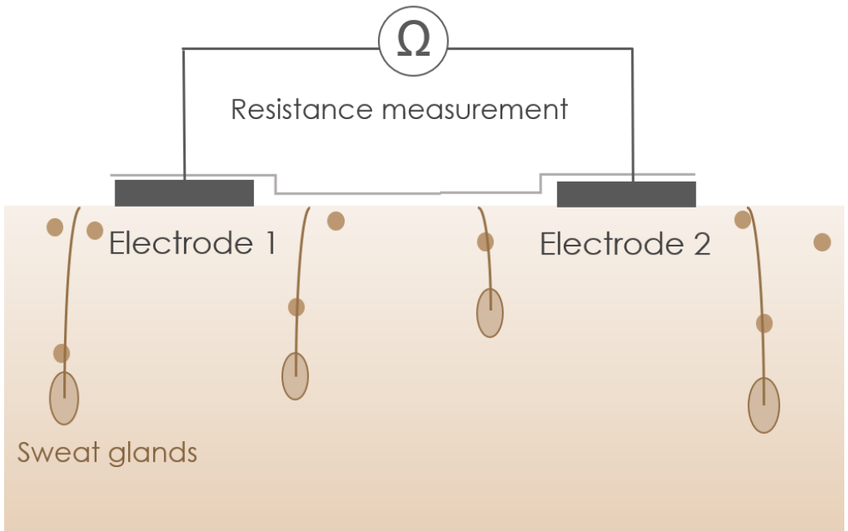


Figure 5: Measurement principle of the EDA sensor

METABOLIZATION TRACKING

Besides the vital data monitoring, SiMA is capable of measuring antibiotic metabolization. At the beginning of an antibiotic therapy it is often not clear which exact antibiotic should be used. Therefore, it is important to monitor the metabolization of antibiotics during the therapy, to detect as soon as possible if the medication has the desired effect or not. Moreover, the metabolization of any drug is different for every patient. Nowadays, the doctor usually determines the dosage of the antibiotic based on superficial criteria such as age, sex and weight. In fact, there are a lot more factors that have to be taken into consideration, for example the body fat content or the presence of specific enzyme variants that break down antibiotics and other drugs at different rates. Since this is hard to measure beforehand it is important to control the dosage throughout the therapy. With the use of SiMA we can additionally define the end of the therapy individually. While a too long use of antibiotic leads to loading of the kidney and the liver, a too short therapy can promote the development of multi-resistant germs. Within SiMA, the metabolization monitoring is done using sweat sensors, which are placed at the bottom of the wrist of the patient as can be seen in the picture below. [21][22]

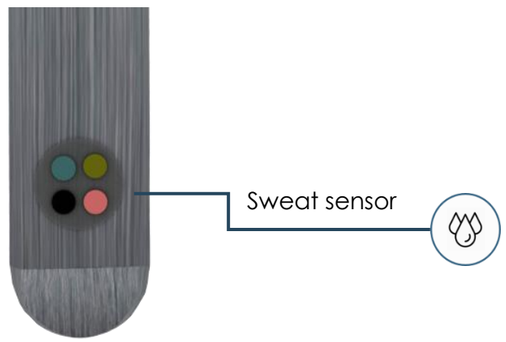


Figure 6: Sweat sensor of the SiMA bracelet

SWEAT SENSOR

Sweat glands are spread all over the human body and are not only involved in perspiration but also in the excretion of drugs and their metabolites. Due to this, sweat is of high interest for medical research and diagnosis and is therefore called the digital biomarker of the future. It is already possible to detect a huge variety of substances within the human sweat including glucose, hormones, lactates, electrolytes such as sodium and potassium and even certain antibiotics including β-lactams and quinolones. Even though, sweat analysis is not widely used nowadays which is mainly due to the lack of accuracy of the current sensors. [23][24]

For SiMA we plan to develop a new sweat sensor that is capable of detecting antibiotics and its metabolites at a high accuracy, To get the needed amount of sweat for the analysis we will use iontophoresis to stimulate the sweat glands to produce more sweat. To do this, a small current will be applied to the skin, which will be, of course, not harmful for the patient at all. The so produced sweat will then be in-situ analyzed using different sensors. The system will be capable of measuring antibiotics and its metabolites as well as electrolytes and hormones. To do this, the sensors include different receptors that can bind specific molecules. This will force an electrochemical reaction that can be measured and then be analyzed to determine the concentration of the different analytes. A schematic description of the measurement principle can be seen in the picture on the next page. [25]

Measuring antibiotics and its metabolites is important to analyze the specific metabolization of the body, while electrolytes and hormones will be monitored to get a deeper insight into the health status of the patient. For example, a high concentration of the hormone cortisol can be an indicator for a high stress level of the patient while an unbalanced electrolyte household can be an indicator for the need of supplements. All this will help us to perfectly adjust the therapy to the patient's needs.

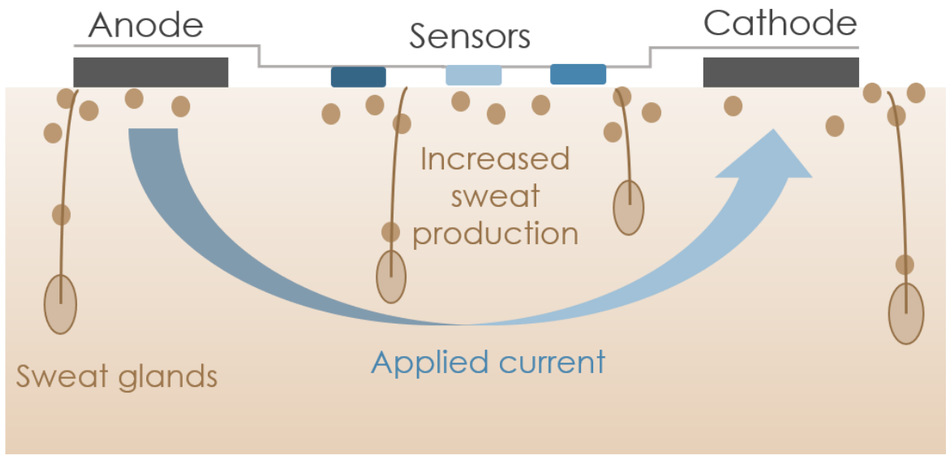


Figure 7: Principle of the sweat sensor

TRANSDERMAL PATCH

The Transdermal Patch is another component of the SiMA System. It can be described as a smart device which is responsible for the regulation and adjustment of transdermal drug delivery. The active ingredient is absorbed through the skin and distributed throughout the body via the bloodstream.

Consisting of several layers that interact with each other, the SiMA patch enables optimal transdermal absorption. Furthermore, it will be designed in such a way that the user is constrained as little as possible. With the size of only about 5 cm in diameter and a height that corresponds approximately to the width of the small finger, the patch is hardly noticeable and can easily be worn under clothing. The structure of the patch in an extended view can be seen in the following figures 8-10.

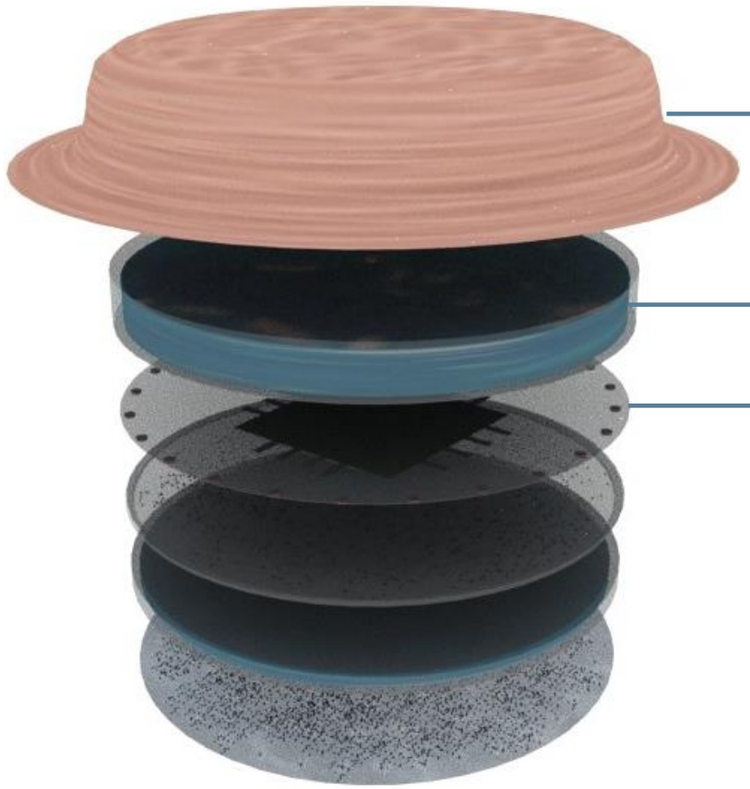


Figure 8: Extended view of the transdermal patch to emphasize the top layers

BACKING LAYER

The backing layer is used as protection against water and sweat for the other components such as electronics and battery. It makes the patch waterproof, so that the patients do not have to think about taking it off and on again when taking a shower.

MAIN RESERVOIR

Looking underneath the protection layer, there is the main reservoir on top which contains liquid medication for the whole treatment plus a reserve. This amount of medicine will be individually calculated due to the body weight and height. The slot for the battery is also located on this level to ensure easy access. It is a small coin cell battery comparable to the batteries used for hearing aids and with the lithium manganese dioxide technology it is high in energy and reliability and sufficient for one treatment, so the user does not have to change the battery [26].

ELECTRONIC LAYER

The battery is connected to the electronic layer which is located directly below the main reservoir. Data transfer from the Data Management Tool to the patch to perform required actions like dosage control and regulation of the next treatment interval is controlled by a microchip.
In addition, the electronic layer includes a ring of infrared LED lights. These serve to heat up metal nanoparticles underneath to a temperature of 40 to 42 degrees. Coming up with this heating function the patch increases the permeability of the skin and allows a better and faster transfer of drug molecules through the skin into the bloodstream. [27]

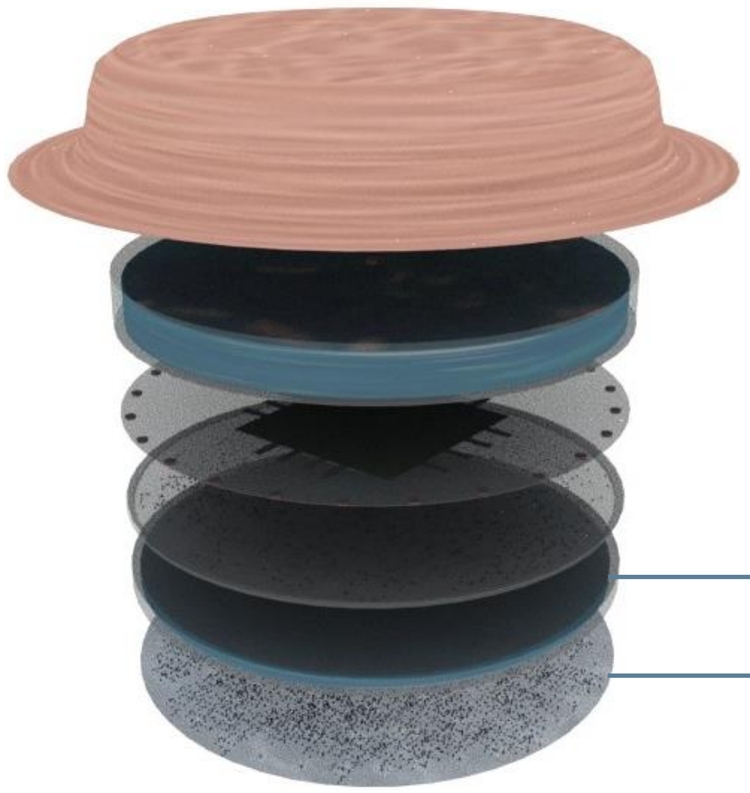


Figure 9: Extended view of the transdermal patch to emphasize the bottom layers

SMALL RESERVOIR

Via a small pipe and regulated by a piezoelectric microvalve, the desired dose for one treatment interval is delivered from the main reservoir to the small reservoir. With the help of this valve, small volumes down to the microliter range can be controlled and as they are particularly energy-saving and have a small and flexible design, they are ideally suitable for the transdermal patch [28].

Depending on the disease and the necessary dose, more or less treatment intervals will be held and the duration of one treatment interval can vary as well.

APPLICATION LAYER

The small reservoir is connected to the application layer, on which LED lights together with a photodiode detect the closest blood vessel and the nearest micro channels, also regulated by small valves, open. Working with the same principle as the photoplethysmography, which is used in the sensor bracelet described previously, the strongest and first reflected signal detected by the photodiode describes the position where the blood vessel has the shortest distance to the skin surface. This special feature provides the best application spot, because it will only be applied to the skin where a quick and safe absorption is possible. Since the patch is not giving the medicine over its whole surface, the skin is not unnecessarily irritated and skin areas underneath the microchannels can recover between the intervals.

Figure 10: Extended view of the bottom side of the transdermal patch

ADHESIVE LAYER

In combination with the application layer, the adhesive layer with an integrated electronic field forms the bottom side of the patch, that provides attachment and skin contact. With the use of modern technologies for smartphones we want to ensure the skin contact of the patch. It works similar to a capacitive touch screen where the position of the contact of the finger evoke a change in the electric field due to the human-body conductance. [29]

As this change is measurable, the patch is able to communicate via the Data Management Tool whether the patch sticks to the skin or not. It is now possible to react accordingly and activate the patch if skin contact is made or disable the patch and stop giving medicine when not. Furthermore, the doctor and the patient will be notified about the changes and actions via the SiMA App.

DRUG PROPERTIES

Various requirements are linked to the physical and chemical properties of drugs that are suitable for transdermal delivery. The substance should be lipid-soluble, but also have a certain solubility in aqueous media. Therefore, the molecular weight has to be below 1000. [30]

DATA MANAGEMENT TOOL

The last component, completing the concept of SiMA, is the Data Management Tool. Its main responsibilities are the data storage and analysis as well as managing the data flow of SiMA.

DATABASE

A database will store data about diseases, causes, medication, treatment course and success. A part of this dataset will be collected prior to the release of SiMA through stakeholder research like interviews of doctors, pharmacists and patients as well as already existing pharmaceutical research papers and databases. The second part will be gained through SiMA once it is implemented and being used by patients. The database will be extended by digital medical history records of all patients registered for SiMA.

DATA FLOW

When a patient is prescribed SiMA for the first time a connection to this patient's digital medical history record will be established. Also, each patch and bracelet own a unique identification number, those can be linked to each other when the patient picks up SiMA at the pharmacy. Because of the Identification Number it is possible for the patient to either bring his own bracelet lent one. Furthermore, more than one patch can be linked to the bracelet like this. Once the patient has attached both the bracelet and the transdermal patch to his body an activation signal will be sent to the Data Management Tool. Now the Tool can receive sensor data about the vital parameters from the bracelet. After the analysis of the sensor data the newly determined dosage information for the next treatment interval will be sent to the transdermal patch.

Additionally, there is a warning system in place if the patch or the bracelet is removed or both components are too far away from each other they will sent out a warning signal to the Data Management Tool. The warnings will be processed here and forwarded to the App. The mobile App for the patient will receive educational tips about the wrong handling of SiMA and how this might affect therapy success. The desktop App of the doctor will also receive an alarm in severe cases of wrong handling, for example removing the SiMA components for several hours.

The App for the patient will furthermore receive updates on vital parameters and therapy progress from the Data Management Tool, as well as helpful therapy tips. Apart from receiving information about the patient's vital parameters and therapy progress, the doctors App will be alarmed by the Data Management Tool in case of side effects or suspicious events. The doctor will then be able to adjust the therapy manually, this information will be sent from the App, through the Data Management Tool to the patient's transdermal patch. The Data Flow of SiMA, visualized in figure 11, will be implemented through MQTT Message Brokers. We are convinced that the Internet of Things will be well established in 2030 and that therefore a constant internet access can be guaranteed either through sim cards for devices or nationwide wireless internet.

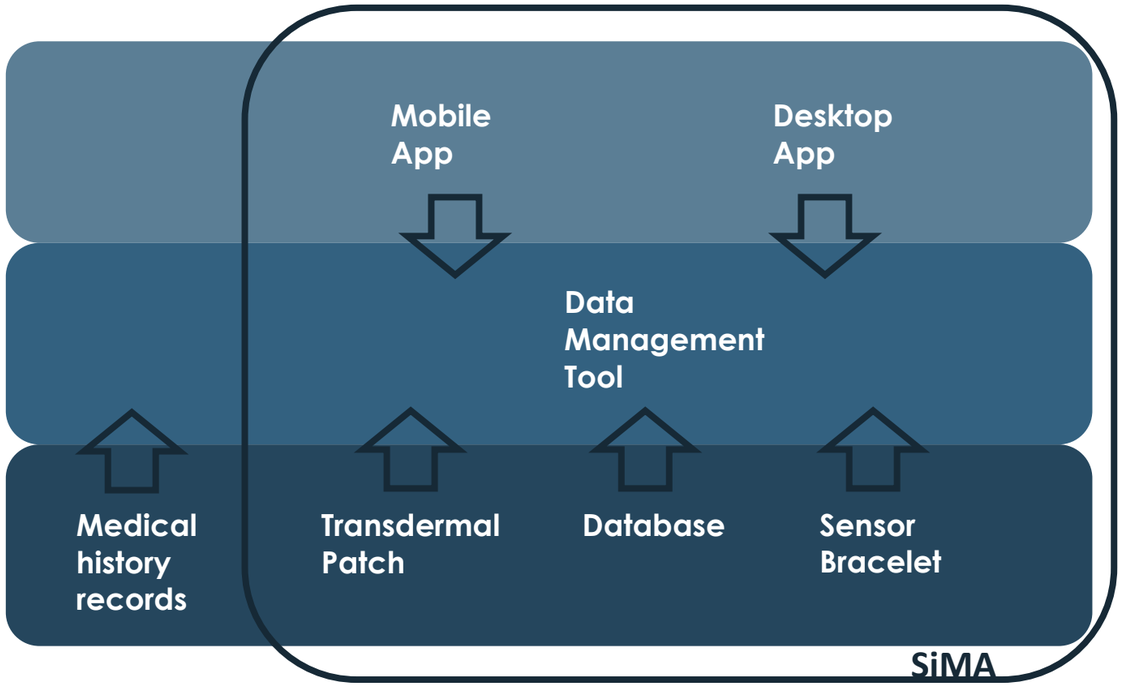


Figure 11: Data Flow of SiMA

DATA ANALYSIS USING CERN TECHNOLOGY

After receiving the raw sensor data from the bracelet, the first step of the analysis is to read out the vital parameters using digital filters. Next the current health status and therapy progress is determined. Based on this information the dosage for the next treatment interval will be specified. The second step of the analysis process is to detect known side effects, suspicious events or a deterioration of the patient's health.

In order to perform this complex analysis CERNs ROOT Data Analysis Framework will be integrated in the Data Management Tool of SiMA. ROOT includes the Toolkit for Multivariate Data Analysis, which provides a machine learning environment. This will allow our system to be trained with various vital parameters as input data, to classify side effects as well as therapy success and failure. The goal is to detect side effects and treatment errors early and adjust the therapy accordingly to prevent them. Furthermore, unsupervised learning can be used to optimize the therapy outcome and the correct dosage for the users' current health status and fastest route to recovery can be determined automatically. We choose ROOT as framework for analysis and numeric computing as it sets itself apart from other systems through its ability to process high amounts of data rapidly. In addition, ROOT is extendable through numerous libraries, including GUIs, Databases and Neural Networks. Therefore, ROOT can not only be used to analyse and learn from the collected data, but also to store and visualize it. [31]

DATA SECURITY

SiMA obviously handles a lot of sensible personal information about its patients, therefore Data Security has a high priority. To access any information on the App, mobile or desktop, 2-factor identification will be used. The patient uses the fingerprint sensor on his bracelet to verify his identity. The doctor will verify his identity through a biometric sensor of his choice which is integrated in his work computer. As the Windows Biometric Framework already supports the easy plugin and use of biometric sensors, such as fingerprint or iris scanners today, we are convinced that this will not pose a problem in the future [32]. SiMA uses biometric identification instead TANs to reduce login time in case of an emergency. To encrypt the Login information of the SiMA users, it will be hashed using algorithms like MD5 or SHA-2 [33].

To protect the transmitted data from Man-in-the-middle attacks in unsecure networks the asymmetric encryption Rivest-Shamir-Adleman (RSA) algorithm will be used. RSA is a public key algorithm, which is widely used in business and personal communication sectors. For the generation of the needed asymmetric keys a Diffie-Hellman key exchange will be performed. [33], [34]

VALUES OF SiMA

STOP
the further development of multi-resistant germs

REDUCE
stress and effort of medication for the patient

PERSONALIZE
therapy and react to side effects immediately

SUPPORT
people to use antibiotics in the right way

PREVENT
side effects of common antibiotics

ENABLE
the doctor to have more time for his patients by preventing checkup visits

SUPPORT
the pharma industry in future drug development by providing data about the effectiveness and side effects of their current medication

LOWER
the expenses of health care insurances by using less medication while causing less side effects

IMPLEMENTATION

To make SiMA become a reality we developed a detailed implementation roadmap that you can see in figure 12. As soon as possible we want to start with research and data collection on which parameters have an influence on the effectiveness of our antibiotic therapy and which parameters are crucial to determine whether the patient is getting better or not. To do this, we want to extract data from already existing studies and clinical research as well conducting own research. This will include expert interviews with doctors, pharmacologists and medical researchers. Also, we want to talk to patients so that we never leave out the people we are actually designing for. Since this data will be essential for our success, we want to start data collection as early as possible to get the highest amount of information.

What is moreover highly important at the beginning is to think about funding. For this, we first want to start a collaboration with the pharma industry. Since we are no experts in pharmacology, this partnership will help us a lot regarding the development of transdermal antibiotics. For SiMA we need an antibiotic that has a small enough molecule structure to be able to be absorbed transdermal. In fact, this is not true for any of the existing antibiotics. Science is making great progress with the development of new antibiotics with the help of AI, which by now already lead to a new antibiotic [35]. Due to this we belief that with the help of the pharma industry and research as well as with the help of artificial intelligence it will be possible to develop a transdermal antibiotic by the year 2030. By helping us achieving this goal, the pharma industry will benefit from a huge amount of data about their drugs as soon as SiMA is fully developed. Since SiMA is monitoring the health state of the patient continuously throughout the whole therapy, this data can be used to track the effectiveness of the medicine used and it will moreover record any side effect the patient has throughout the therapy. This data can help pharma research to develop new and better drugs in the future.

As a second financing method we want to apply for government funding. In the year 2015 the Federal Ministry of Health of Germany, together with the Federal Ministry of Food and Agriculture and the Federal Ministry of Education and Research developed the German antibiotic resistance strategy that is called DART 2020. This strategy aims to stop the further development of multi-resistant germs while tackling all causes of the development within medicine, agriculture and the food sector. To achieve this, the federal republic of Germany has already started campaigns to raise the awareness for this topic within the society, but they moreover what to support research in this area. This is where we want to step in. Since our overall goal is to stop the development of multi-resistant germs, we believe that the federal republic of Germany will support us financially. [36]

The next steps are closely interlinked and merge into one another since it is now time to get started with the real development. First, we want to set up our database and server to store all the data already collected by our research and make them accessible whenever it is needed. Then it is time to really get hands on and start prototyping. For the bracelet this will include testing different sensors for the vital data monitoring and integrating them into a bracelet. Since there are already a lot of fitness trackers and wearables on the market, we can easily get inspiration. Prototyping for the transdermal patch will be a lot more difficult and time consuming because SiMA will be very different compared to already existing transdermal patches. But this will make this step even more exciting for us.

While developing, we always want to include the user as well to get the best user experience in the end. For this, we will design the user interface for the patient and the doctor so that the usability testing can be done.

After all components are created separately, they all need to be connected to our data management tool as a next step. This will enable the doctor and patients to access the vital data measured by the bracelet but will also make it possible to communicate with the patch remotely. Before the first SiMA versions can enter the market, only the regulatory approval needs to be done.

By the year 2025 we want to place our first SiMA version on the market. The SiMA bracelet will be capable of tracking vital parameters, which are analyzed by our data management tool and are made accessible for both the patient and the doctor. The patient on the one hand can stay in touch with his health and the doctor on the other hand can get access to more data about his patient which can help him with diagnoses enable him to check the therapy success of his patients. The first version of the SiMA bracelet can therefore function as a health state tracker that can be worn during everyday life with the advantage of wider analysis compared to already existing ones and the additional connection to the doctor. Moreover, the first bracelet version can be worn in combination with the early SiMA patch.

This first version of the SiMA patch can be used with already existing transdermal medication, for example with drugs for pain therapy. This patch will already include the micro channels and it will be able to detect the best application spot. The dosage can already be personalized as well, but it is yet not automated, but the adjustments can only be done remotely by the doctor.

Our first product versions will not only enable us to gain more money for further development but will also help us to collect a lot more data, and now even from our own products and sensors. For this, we will additionally include the sweat sensors to our bracelet as a next step. Since all sensors are included to the bracelet at this point, we can now gain data that can be prepared to be used to train the neural network within our data management tool. This step is necessary to teach the system how to adjust the dosage automatically.

Now the only thing that is missing is the transdermal antibiotic. On average, it takes about 15 years for a new antibiotic to be developed, which would be a too long time for SiMA to be accessible for antibiotic treatment by the year 2030 [37]. But due to the fact, that we actually do not need a complete new antibiotic, but it is only necessary to change the molecule structure of the already existing ones, we believe that all this can be done within 10 years. Additionally, the SiMA patch can already be used for Phase III testing of the new antibiotic. This is the part of medicine development when the new drug is tested with a huge group of sick patients to prove its effectiveness and to identify possible side effects [38]. After the drug has passed all tests, there is only the regulatory approval missing until it can finally be sold on the market.

At this point we reach the year 2030 and the fully automated and personalized antibiotic therapy using the SiMA system will be available on the market. Of course, we will then conduct a post market surveillance of our product, so that it can be constantly optimized.

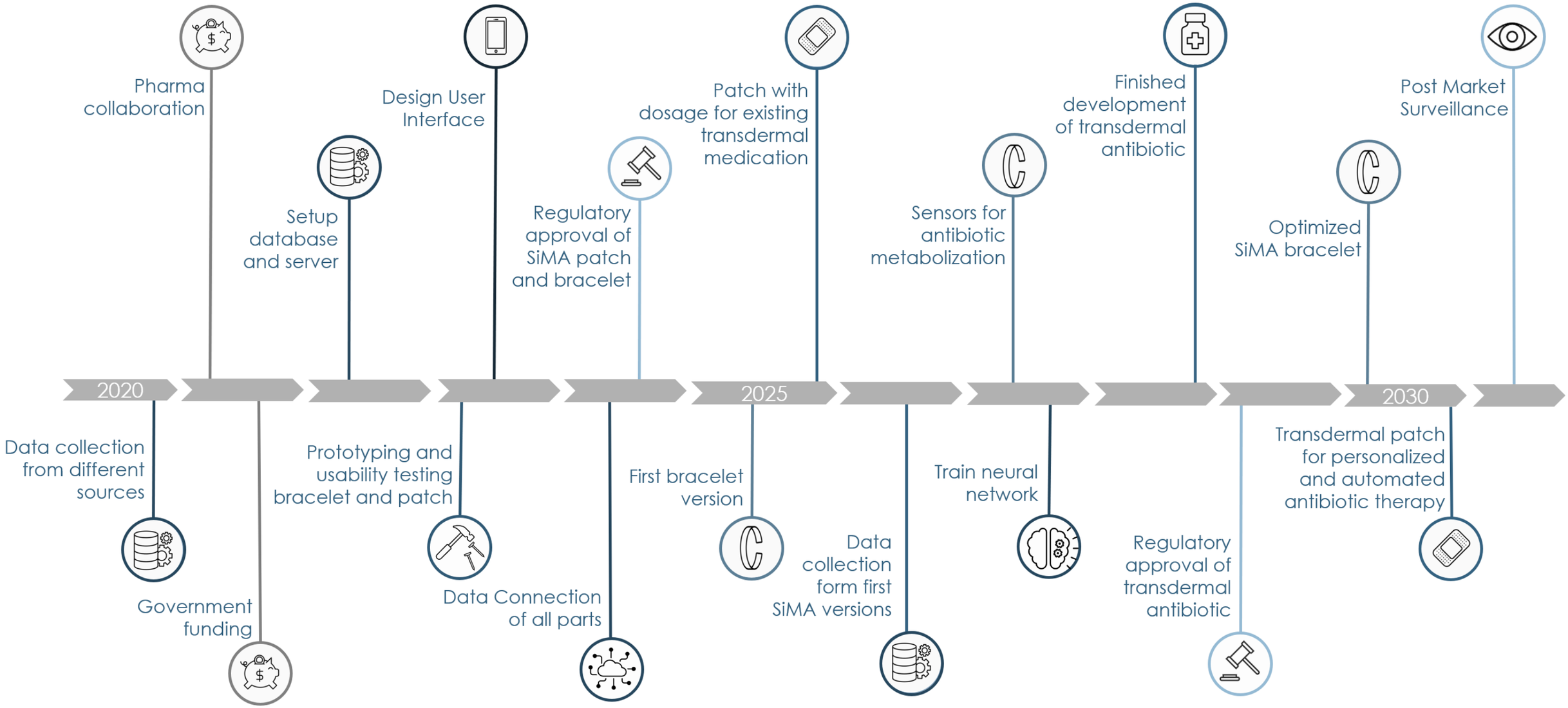


Figure 12: Implementation Roadmap

FUTURE IDEAS

Our vision for SiMA lasts much further than only until the year 2030 and there is a lot more potential in our ideas besides tackling the development of multi-resistant germs. Let's see how far your imagination can go.

Can you imagine a world …

… where your body is automatically provided with all vitamins and supplements needed to be most healthy and active?

… where elderly people are given all medication automatically so that they will never be able to forget their pills and family and care takers have more time to really take care of their loved ones?

... where kids and babies get their needed medication without noticing?

… where all chronical diseases can be treated automatically and according to the actual health state of the patient?

… where medication therapy in hospitals is completely automated and nurses and care takers have more time to actually take care of the patients?

… where a digital tool can help the doctor in finding a diagnosis by analyzing the health records of the patient?

… where your health tracker can predict your sickness before you even feel it?

We can imagine all this, and we hope you do as well, so that together we can make the world a better and healthier place in the future!

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