Clinical Trial Protocol - Baby Fever Monitor (BabyFM)

Name of the clinical trial: **"TELEMEDICINE SYSTEM TEST FOR THE CONTINUOUS BODY TEMPERATURE MONITORING IN ADULTS - A PILOT STUDY"**

This protocol has been prepared in accordance with the international standard EN ISO 14155, Clinical trials of medicinal products for humans - Good clinical practice; Annex A (normative) Clinical Trial Plan (CIP).

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Contents

1. SUMMARY OF CLINICAL TRIAL PLAN 6
2. PRINCIPAL INVESTIGATOR'S STATEMENT 9
3. BACKGROUND AND RATIONALE 10
4. IDENTIFICATION AND DESCRIPTION OF THE TESTED MEDICAL DEVICE 12
    1. Brief description of the tested medicinal product and its purpose 12
    2. Details of the manufacturer of the investigational medicinal product 14
    3. Name of medical device and software version 15
    4. Description of medical device traceability procedures 15
    5. The purpose of the investigational medicinal product in the proposed clinical trial 16
    6. Population and indication for which the investigated medicinal product is intended 16
    7. Description of the materials from which the medical device is made 16
    8. Device training and experience 19
    9. Procedures for the use of a medical device 19
5. CLINICAL TRIAL DESIGN RATIONALE 20
    1. Preclinical evaluation 20
    2. Evaluation of clinical data from the literature 20
    3. Explanation for tracking time 21
    4. Explanation for the selected study population 21
6. RISKS AND BENEFITS 22
    1. Expected benefit 22
    2. Expected side effects of the device 22
    3. Residual risks associated with the medical device 23
    4. Risks associated with participation in a clinical trial 23
    5. Possible interactions with concomitant medical treatment 23
    6. Steps to be taken to control or mitigate the risk 23
    7. Risk and benefit rationale 24
7. OBJECTIVES AND HYPOTHESES OF THE TEST 27
    1. Primary and secondary goals 27
    2. Hypotheses 27
    3. Claims and performance of the medicinal product to be verified 27
8. STUDY DESIGN 29

1. General 29
1. Brief description of the study 29
2. Measures to avoid bias 30
3. Primary and secondary outcomes 30
4. Methods and time for assessment, recording and data analysis 31
5. Respondent replacement 31
2. Tested medicinal product and comparator 31
1. Description of investigated medicinal product and comparator usage 31
2. Justification of the choice of comparator 32
3. Other medical devices or drugs that will be used during the clinical trial 33
4. The number of investigational medicinal products that will be used in the clinical trial 33
5. Maintenance and storage of the medical device 33
3. Respondents 35
1. Inclusion criteria 35
2. Exclusion criteria 35
3. Criteria and procedures for withdrawing subjects or discontinuing participation 35
4. Recruitment of respondents 36
5. Place of examination 36
6. Total expected duration of the clinical trial 36
7. Expected duration of participation of each respondent 36
8. Estimated number of included respondents 37
9. Estimated period of inclusion of respondents 37
4. Procedures 37
1. Procedures to which respondents are subjected 37
2. Sponsor Responsibilities 41
3. Factors that may affect the outcome of a clinical trial or the interpretation of results 41
5. Monitoring plan 42
9. STATISTICAL DATA PROCESSING 44
1. Description of statistical methods 44
2. Sample size 44

3. Significance level 44
4. Missing data 45
5. Patient populations and subpopulations 45
6. Interim analysis 45
7. Deviations from the statistical plan 45
8. Analysis of special groups of subjects (populations) 45
10. DATA HANDLING 46
1. Test sheet for collecting data about the respondent 46
2. Source documents 47
3. Data management 47
4. Confidentiality 47
11. AMENDMENTS TO THE PROTOCOL 48
12. DEVIATION FROM THE PROTOCOL 49
1. Statement of Deviation from the Clinical Trial Plan 49
2. Recording, reporting and analysis of CIP deviations 49
3. Notification Requirements and Timeframes 50
4. Corrective and preventive measures and criteria for disqualification of the principal researcher 50
13. RECORD OF USE OF MEDICINE DURING A CLINICAL TRIAL 51
14. DECLARATION OF CONFORMITY 52
1. Ethical principles 52
2. Financing and insurance 52
3. Provision of emergency medical assistance and assistance due to the occurrence of other adverse events 52
4. Declaration of Helsinki 53
5. Good clinical practice guidelines 53
6. Approval of the study by the Ethics Committee 53
15. INFORMED CONSENT PROCESS 54
1. Description of the general process of obtaining informed consent 54
2. Informed consent in special circumstances 55
3. Participant confidentiality 55
16. ADVERSE EVENTS, ADVERSE EFFECTS OF THE DEVICE AND DEFECTS OF THE DEVICE 57

1. Adverse event (AE) 57
2. Adverse Device Effect (ADE) 57
3. Device disadvantages 57
4. Serious Adverse Event (SAE) 57
5. Serious Adverse Device Effect (SADE) 58
6. Unintended Adverse Device Effect (UADE) 58
7. Reporting of adverse events 59
8. SAE / SADE / UADE application procedures 59
    1. SAE reporting authority 59
    2. Reporting of serious adverse events (SAEs) by investigators 59
    3. Reporting an adverse event to a regulatory body 60
    4. Reporting of adverse events 60
9. Device defect reporting process 60
10. List of expected adverse events and expected side effects of the device 60
11. Security Data Oversight Board 61
12. Interim analysis 61
17. VULNERABLE GROUPS 62
18. SUSPENSION AND/OR EARLY TERMINATION OF THE CLINICAL TRIAL 64
19. ACCESS TO CLINICAL DOCUMENTS 65
20. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES 66
1. General considerations 66
2. Training 66
21. HUMAN RESOURCES INCLUDED IN THE STUDY 67
22. CLINICAL STUDY REPORT AND PUBLICATION OF RESULTS 67
23. LITERATURE 68

1. SUMMARY OF CLINICAL TRIAL PLAN

Procol Number	BABYFM-010
Version	3.0
Title	TESTING THE TELEMEDICE SYSTEM FOR CONTINOUS FEVER MONITORING IN ADULTS – THE PILOT STUDY
Phase	*First in Humans* / Pilot proof of concept
Indication	Fever (high body temperature)
Name of device	Baby Fever Monitor (BabyFM), temperature sensos with cotton band for fixation, class IIa
Manufacturer	Baby FM DOO, Veljka Dugoševića 54, Belgrade, Serbia
Time in use since the study start	0 days
Aims	Primary aims: - Efficacy –accuracy of temperature measurements - Safety - absence of side effects on the skin due to the sensor and/or addition of cotton fabric contact with the skin - Performance of the device - adequacy of the function of the system itself (connection with the phone, temperature measurement, continuity of the connection, adequacy of the software functioning) Secondary aims: - Comfort during wearing the sensor with a cotton strip - Anxiety due to constant measuring of the body temperature and wearing the wearable device
Study design	This is a non-randomized, diagnostic, single-center, pilot study with one group of subjects with the aims to examine the efficacy and safety of a telemedicine system for continuous body temperature measurement in adults. Up to 40 subjects will be enrolled in this phase of the clinical trial. No stratification, nor randomization of subjects is planned for this trial. Subjects who meet inclusion criteria will be monitored for up to 72 hours plus 72 hours after removal of the device. Namely, the device will be placed on their body and will be there for up to 72 hours, and then it will be removed. The test subject will be monitored for an additional 72 hours by the team in charge of the test, for possible side effects. The test subjects will have a sensor placed in their armpit or on a position slightly below on their side, which will be connected to a mobile phone. This device continuously measures body temperature in the measuring position. A member of the research team (principal researcher/co-researcher/nurse) measures the temperature of the skin in the opposite axillary pit manually, i.e. with a gallium thermometer and records it every 30-60 minutes. When the body temperature begins to rise, a member of the research team takes the body temperature for 15-30 minutes. After reaching a stable temperature, the temperature is measured every 30-60 minutes. If the subject is given drugs to lower the body temperature, the body temperature is measured again every 15-30 minutes until the temperature stabilizes to a normal subfebrile state. Medicines given are recorded, including the time they were given.
Follow up	Each respondent will be included in the study for a maximum of 144 hours (6 days). In fact, the subject wears the device for up to 72 hours (in 8 hours cycles), and then, at the end of the follow up, the device is removed from the subject, and then the subject fills out the questionnaire. The subject will be monitored for another 72 hours after removing the device for possible side effects.

Total study duration	The expected duration of the clinical trial, which includes the recruitment and monitoring of subjects, is anticipated up to 4 months. After the follow-up of the last recruited patient is completed, the research site will no longer recruit subjects or follow up subjects further and then, data cleaning will be undertaken. The estimated time for cleaning data and entries in the electronic database is up to 30 days from the end of the monitoring period, the last one recruited respondent.
Site	The study is monocentric and will be conducted at the University Clinical Center of Serbia, Pulmonology Clinic
Outcomes	Primary outcome: - Efficiency - agreement between the temperature values of the standard temperature measuring device and the telemedicine system for body temperature continuous monitoring - Safety - frequency of adverse events due to the contact of the device with the skin of the patient with the telemedicine system for body temperature continuous monitoring - Performance - whether the device works in real conditions, whether it measures body temperature and whether the software adequately informs and alarms the user Secondary outcomes: - Anxiety - how safe and less tense the patient feels if there is continuous monitoring of vital parameters during a febrile episode - Patient comfort measured by a short Questionnaire with questions about user experience while using the continuous temperature measurement system
Enrollment criteria	Inclusion criteria: - Consent to participate in the study - A person of male or female sex - Age 18 and above - Ability to measure the patient's body temperature frequently - Persons who have been hospitalized due to any type of infection or any other disease that results in fluctuating body temperature (increase, decrease) - Completed all potential diagnostics of the hospitalized patient (no interrupting the measurement of the telemedicine device) Exclusion criteria: - Allergic to plastic or silver contact - Anatomical anomalies that prevent the placement of the system - High-risk health conditions, hospitalized in intensive care unit - A pacemaker or other device on the skin or implanted in the body that emits electromagnetic radiation
Sample size	This is a pilot study, exploratory in nature, the first on humans. The sample size was determined based on the formula for calculating the sample size and on the basis of recommendations from existing studies. It is a non-invasive measurement, minimal risk and short exposure. A sample of 40 subjects will be included in the study. If the agreement is high, the study of 40 respondents has a study power above than 80% using type I error alpha=0.05 to assess a significant correlation between the tested and the standard measurement method greater than r=0.8.
Statistical analysis	Descriptive and analytical statistical methods will be used in this study. Absolute and relative numbers (n, %) will be used for attributive variables, while measures of central tendency (arithmetic mean, median) and measures of dispersion (standard deviation, interquartile range, variation interval) will be used for numerical variables. All descriptive parameters will be shown with 95% confidence intervals. The diagnostic accuracy of the device will be tested by analyzing the agreement of the two methods. Absolute values of temperature will be tested by correlation analysis (Pearson's correlation) and interclass correlation (ICC). The graphical agreement of the absolute values

	will be shown using a scatter diagram or a Bland-Altman diagram.

2. PRINCIPAL INVESTIGATOR'S STATEMENT

I, the principal investigator, hereby guarantee that the above-mentioned clinical trial will be conducted in accordance with the Clinical Trial Plan (including possible amendments that will be documented), the Good Clinical Practice (GCP) guide, i.e. the standard for clinical trials of medicinal products on humans (ISO 14155) and according to the requirements of the applicable laws of the Republic of Serbia.

I hereby declare that I am familiar with the purpose of the trial, the Clinical Trial Plan, the tested medical device, as well as the safety profile of the tested medical device. The informed consent form will include the elements necessary to obtain consent according to the Declaration of Helsinki and all its revisions.

All participants (responsible for the design and conduct of this clinical trial) will complete participant protection training before interacting with any participant or before accessing their confidential data collected in this clinical trial.

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, members of the research team, the Agency for Medicines and Medical Devices of Serbia, and members of the Ethics Committee of Serbia, unless authorized by the Sponsor.

I declare that I have no potential or actual conflict of interest and that I agree to the terms and conditions related to this clinical trial as defined in this Clinical Trial Plan, Test Lists (CRF) and all other documents related to the Clinical Trial Plan. I also declare that there is no financial interest or agreement of a financial nature, where the amount of compensation would depend on the outcome of the investigation; that there are no payments of any other type, except for the payments defined in the contract with the sponsor of the clinical trial; that there is no financial interest in exercising the patent rights of the examined medical device or interest in terms of ownership of capital related to the Sponsor, such as interest in the form of share ownership, as well as any financial interest in ownership that cannot be proven by viewing public information.

Principal Investigator: Ass. Dr. Nataša Đurđević, internist, pulmonologist

Date 29-FEB-2024

Name and address of the examination site: University Clinical Center of Serbia, Pasterova 2, Belgrade, Serbia

3. BACKGROUND AND RATIONALE

According to current clinical guidelines recommends axillary temperature measurement as the standard practice for detecting elevated body temperature, particularly during febrile illnesses. Nowadays, the digital axillary thermometer is broadly accepted as the gold standard for home-based and outpatient temperature assessments.

Continuous monitoring of babies' body temperature in real time would avoid a lot of problems and mistakes caused by parents and caregivers. The telemedicine system enables the setting of a temperature alarm as well as a warning system (notification), monitoring with two or three devices, notification of medication dosing and reporting to the pediatrician.

Studies show that medication errors occur every 8 minutes among children in the US (non-hospital setting), while in the case of errors in infants and children under the age of 6, it is the most common error by parents.

Mistakes by parents who have a baby for the first time are more common, parents feel insecure and seek pediatric support.

Sleeping deprivation, stress and unpredictable situations are the main problems of parents who face episodes of elevated body temperature of their babies during the night, which affects their productivity at work.

Existing temperature monitoring devices frequently rely on rely on adhesive patches for sensor fixation. However, the adhesives often cause local skin reactions such as contact dermatitis or allergic responses in infants. While non-adhesive systems are safer for the skin, they generally provide less accurate temperature readings due to suboptimal sensor placement and intermittent contact.

The central unmet need is for a device capable of accurate, continuous, real-time temperature monitoring that ensures optimal infant safety and offers parents reassurance and uninterrupted rest.

In addition, such systems facilitate the monitoring of therapeutic administration, thereby reducing the risk of dosing errors caused by parental fatigue. While maintaining parental productivity following a febrile episode is a secondary objective, it remains highly relevant for working parents. Furthermore, automatically generated temperature reports exported from the application can support parental communication with pediatricians, enhancing the accuracy of therapeutic decision-making particularly valuable during pandemic conditions and for families residing in rural areas.

The problem was defined and confirmed through work with focus groups. Based on their assessment of the functionality of the continuous temperature monitoring system, it was concluded that it is necessary:

- continuous temperature monitoring with notification and warning system
- prevention of errors in drug dosing with notifications and reminders for drug doses
- remote monitoring on several devices (double control when the baby is with the

babysitter or someone else)

- body temperature trend report (including graphic display) for easy communication with pediatricians
- question and answer section with temperature guidelines from pediatricians
- anti-allergic material for children's skin

To overcome the problem of skin contact, the new system has an elastic cotton band that does not irritate the baby's skin, which is also easy to maintain and wash and can be reused (designed to stay in the axillary position and not harm the baby's skin).

In order to conduct research on babies, it is necessary to conduct research on adults first. The clinical trial plan envisages testing the system in adults (this trial) and testing the system in children.

At the Pulmonology Clinic of the University Clinical Center of Serbia, a pilot study will be conducted on adults, so if the system proves to be effective and safe, the next clinical trial will be conducted on children.

4. IDENTIFICATION AND DESCRIPTION OF THE TESTED MEDICAL DEVICE

1. Brief description of the tested medicinal product and its purpose

The tested medical device, Baby Fever Monitor (Baby FM), is a temperature sensor with a support that is used for continuous measurement of body temperature. It consists of a temperature sensor, software for mobile devices, a silicon flat thermoconductive box and a carrying strap. The temperature sensor is a high-sensitivity sensor with an accuracy of <0.1ºC, and is housed in a silicon flat thermoconductive box. The maximum diameter of the electronics box is adjusted to the size of the device's battery (CR2032). A wearable strap, similar to spinal correctors, is made of pure cotton or a high proportion of cotton and designed specifically to fix the sensor box in the axillary position. A small pocket belt on the inside of the hip strap is designed to accommodate the sensor box. The tape can be washed after several episodes of temperature measurement. The sensor box can be easily removed from the belt pocket belt and put back (in case of washing and cleaning of the belt). Cotton straps (straps) can be adjusted to accommodate different age categories, i.e. constitution.

The system measures temperature in a position that is standardized for temperature measurement (axillary position). The elastic sensor band covered with cotton fibers does not irritate the skin. Easy to remove, clean and install (reusable).

Bluetooth Low Energy (BLE) is used as the transmission protocol for communication between the mobile device and the sensor. In order to achieve the maximum required resolution, the speed of measuring the temperature of the sensor plate is controlled by the software on the mobile phone. The software runs on two operating systems, Android and iOS. The software has several screens. On the main one the user has information about the current temperature measured by the sensor and a graph of the temperature values in the last 12 hours. The application (software) allows multiple sensors to be connected to a mobile phone, but only one can be actively tracked at a given time. The user can set alarms in terms of which temperature value will warn the user that the temperature is higher than the defined one. Also, there is an alarm for interruption of communication with the sensor longer than the defined time. The temperature is measured in resolutions of 0.01 to 1 measurement per second, which enables the trend of the temperature signal, i.e. the trend of the body temperature, to be monitored and determined. All reports and history overview can be exported in PDF.

The sensor features a capacitive module-based interrupt mechanism that triggers device detection without the need for a physical button - which will improve user experience and environmental sustainability.

Using advanced Autoregressive integrated moving average (ARIMA) signal processing will control and automatically check the temperature input and create an additional notification system that will eliminate various unwanted deviations from the real signal.

If necessary, the host <-> sensor communication protocol can be encrypted, and a CRC check is in place to ensure that measurements are received correctly.

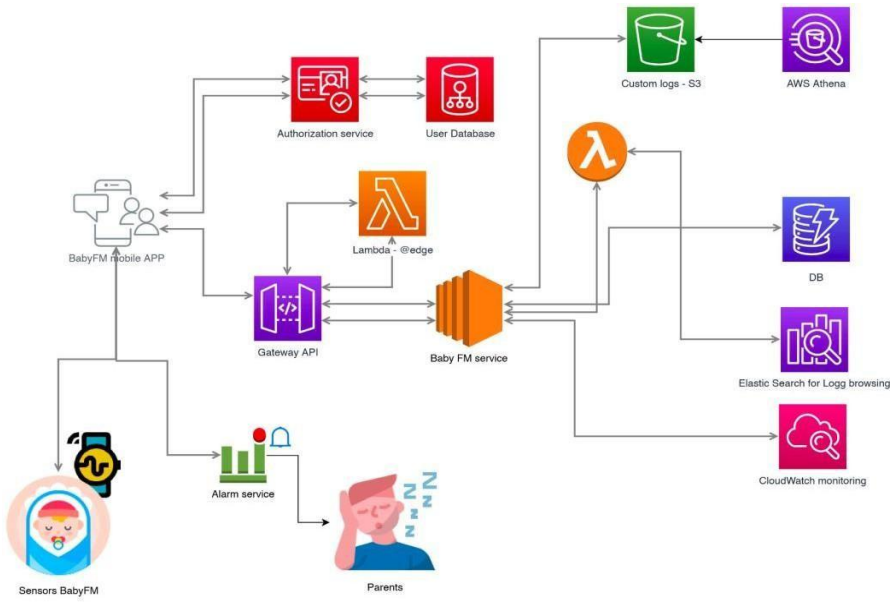


Figure 1. System for continuous monitoring of body temperature - technical overview

2. Details of the manufacturer of the investigational medicinal product

Baby FM DOO is a company registered in the register of companies from 19-5-2021. year.

Director of the company Savo Papić.

The device (electronics) for Baby FM DOO is assembled by the company Iritel AD Belgrade. Iritel, as a manufacturer, meets the following standards:

- SRPS ISO 9001:2015,

- SRPS ISO 14001:2015,

- SRPS ISO 45001:2018,

- ISO/IEC 27001:2014

- SOURCE 9000/21

The application (software) for Baby FM DOO was made by BrigIT.

3. Name of medical device and software version

The device used in the clinical study is called "BabyFM" and the version of the device is "beta 1.0" and represents a test series on the basis of which further (eventual) modification of the hardware part of the device will be carried out.

The software is called “Baby FM” and the current version is “beta v21.13.0”.

4. Description of medical device traceability procedures

For the purposes of the clinical trial, five sensors and forty wearing bands will be produced. Each subject who will be included in the clinical trial will receive one wearable strap (personalized piece of equipment in the clinical trial), while the sensors will not be personalized, that is, during the duration of the clinical trial, one sensor will be used by eight different subjects in different periods of time. All five sensors will be produced in a single batch, but each sensor will be assigned a unique identification number. Also, the tapes will be produced in one batch, and each tape will be assigned a unique identification number. By marking the sensors and tapes, a technical evaluation and identification of possible defects in production will be carried out, in terms of systematic measurement error, mechanical defects, inadequate sensor positioning and similar problems.

The entire number of tested medical devices, intended for the needs of this clinical trial, Sponsor will deliver to the test site before the start of the test. Principal investigator or team member in charge for testing, delegated by the main researcher, will check the quantity of delivered medical devices, check the packaging (whether it is damaged) and document the checked information in the appropriate log (Log for receipt of medical devices). Medical supplies will be stored in a secure location at the test site, in a lockable access-controlled room. The

principal investigator or member of the trial team are responsible for the medical devices during the trial period (see section 13).

5. The purpose of the investigational medicinal product in the proposed clinical trial

The BabyFM medical device is a system for continuous body temperature measurement. The purpose of the mentioned device is to measure body temperature in the axillary position at certain time intervals. For the purposes of the study, the measurement will be done in 10 second intervals, but it can be changed to 30-60 seconds.

6. Population and indication for which the investigated medicinal product is intended

The system for continuous telemonitoring is intended to be used on children under 6 years of age, primarily babies or younger children, so the selection of patients of this age is crucial for testing.

But, as the system must first be tested on adults (not children), then a study must initially be conducted to test the system's effectiveness and possible side effects on adults. Only if the system

proves safe on adults, a second clinical trial is planned to be conducted on children.

For this proposed clinical trial, the subject population consists of adults, male or female, 18 years of age or older who are hospitalized for an illness with febrile episodes.

The indication for which the medical device is intended is elevated body temperature.

7. Description of the materials from which the medical device is made

The device is coated with medical silicone in order not to interact with the subject's skin. The part that houses the electronics (extended part) is harder, but shaped so that there are no sharp edges or structures that can damage the skin. The sensor is located at the top (smaller part at the opposite end) where on one side is a metal plate in the shape of a roller that is positioned on the skin and measures the temperature. The rubberized part that connects these the two parts are also made of medical silicone, only they are flexible and have rounded edges, all in order not to damage the skin during handling.

The wearing strap, designed to keep the sensor in appropriate position, which is in contact with the subject's skin, is made of pure cotton or a high percentage of cotton. The elastic sensor band covered with cotton fibers does not irritate the skin. It is easy to remove, clean and reusable.

The battery in the device is certified with the CE mark, and at this stage, a Duracell battery will be used, which according to the manufacturer's specification guarantees protection against any defect for 2 years from the date of purchase.

The device uses Bluetooth technology for data transmission, which is certified by the SIQ company. Based on the test conducted by SIQ, this device can be used in commercial applications (certificate with test data attached to the protocol).

The device has no pharmaceutical properties because it is not introduced into the body, does not penetrate the skin, and does not release any medicine or similar liquids, gel or powders.

The device is composed of standard components, and each active component has a Federal Communications Commission (FCC) certificate. FCC certification means that the electronic components of the device have been tested according to the FCC standard and are approved for commercial usage. FCC certification does not mean that the device is safe, but that it is within the limits of permissible radiation levels.

Table 1 shows a list of all components with a role in an electronic device and available documentation on the Internet.

Component	Role	Available documentation
Bluenrg-m2sp	Main microcontroller in transceiver unit	https://fcc.report/FCC-ID/S9NBNRGM2SP https://fcc.report/FCC-ID/S9NBNRGM2SP/4229301
TMP117	Main temperature sensor high precision (+/- 0.1C)	https://www.ti.com/lit/ds/symlink/tmp117.pdf?ts=1695650550674&ref_url=https%253A%252F%252Fwww.google.com%252F
CR2023	Power supply (battery)	https://www.duracell.com/wp-content/uploads/2016/03/CR2032JCS0820.pdf
Flex Cable	It provides the connection between sensors and the main board	
Printed board	The mechanical component provides the electrical connection between the components. Mechanically holds components in the fixed positions	
Battery holder	It fixes the battery and secures it connection between the poles	https://eu.mouser.com/datasheet/2/418/9/LNNC_S_A0002913840_1-3237435.pdf
Mechanical Switch	Allows the device to be disconnected from the power supply	
Voltage Regulator	Provides stable voltage device as the battery is running low	
LED Diodes	Indication of trouble on device	

Table 1. Role and available documentation of components

8. Device training and experience

No prior experience is required to measure body temperature with the Baby FM device. As this is a new technology, researchers will be provided with the Baby FM Continuous Body Temperature System User Guide before and during the clinical trial. Also, prior to study start, an initial visit to the trial site will be conducted, during which all necessary training of the principal investigator and other members of the trial team will be conducted, including training on how to use the trial medical device. Training for the use of the investigational medicinal product includes:

- correct positioning of the medical device
- connecting a medical device to a mobile phone via Bluetooth Low Energy
- use of a mobile phone application associated with an investigational medicinal product

The Baby FM device is classified as a class IIa medical device. It is non-invasive and is intended for short-term use but given that this is the first trial in humans, researchers will supervise the subjects involved in this clinical trial. As the subjects are already hospitalized at the site of the investigation, a member of the team in charge of the investigation will be available to subjects for any issues and/or questions during the trial.

9. Procedures for the use of a medical device

There are no specific medical or surgical procedures for the use of Baby FM medical device.

After switching on, the device is placed in the belt according to the instructions that come with the device. At the smaller end, the silver (metal) part should face inward, toward the subject's skin. The smaller tip should be in the armpit, while the larger (hard, pear-shaped part) should be outside the armpit. Once the chest strap is in place, it is necessary to adjust the size for the band by tightening the strap and fixing it. Although the band is elastic and cannot interfere breathing, it is necessary to check whether the band is not too tight by checking if the band can be easily be separated from the body by hand and see how far it is possible to separate the band with a light movement. After adjusting the tape, the researcher should move the tape again within 5 minutes, that is, lift it away from the body and see that it is not too tight by checking if the marks on the skin are deep and if there is any irritation. If everything is in order, the measurement can start. The measurement starts by connecting the sensor to the device using the BlueTooth connection. It is necessary to turn on Bluetooth on the device used to receive the signal and connect it to the sensor. When the temperature value appears on the screen, the user is sure that the sensor is connected and measuring temperature. The maximum distance between the tested medical device and the mobile phone should be 3 m and the device should be in the same room as the mobile phone.

5. CLINICAL TRIAL DESIGN RATIONALE

1. Preclinical evaluation

All devices were subjected to a 3 month monitoring period under controlled test bench conditions to assess potential functional degradation, physical deformation, operational failures, cessation of operation, or related malfunctions. All tested devices worked adequately throughout the monitoring period, without changing their physical properties. No battery leakage was observed. The device does not heat up, does not produce any sound or vibration.

2. Evaluation of clinical data from the literature

There are several studies with the aim to measure body temperature using different innovative technologies. Ogidan et al used a contact-tracing temperature scanner, which uses a wireless sensor and an RFID (Radio Frequency Identification) card to collect and store information about the user's temperature and identity in a remote database, facilitating contact tracing via a secure web interface. Comparative studies indicate that the device works best at a distance of 16 cm, showing a faster response time (0.004 seconds) compared to a mercury thermometer (179.2 seconds), making it advantageous in situations where speed is key, although it shows less accuracy than a contact thermometer (Ogidan et al, 2022).

Khan et al conducted a study of 538 adult patients at the temperature counter and did a sequential sampling. Forehead temperatures were measured first with an infrared thermometer and then with a mercury thermometer, revealing a significant difference in mean temperatures. The correlation between the two methods was weak to moderate, and the infrared thermometer showed variable sensitivity and specificity at different temperature thresholds (Khan et al, 2020).

Eisenkraft et al have shown the clinical relevance of continuous and prolonged body temperature measurement is essential for certain health conditions, and the "dual sensor" technique, combining a wireless skin temperature sensor with a heat flux sensor, provides a valuable and simple method for frequent monitoring. Two clinical studies comparing this technique with oral and body skin temperature measurements using medical thermometers in different scenarios showed high correlations and minimal biases, proving the effectiveness and reliability of the "dual sensor" method in different patient groups (Eisenkraft et al, 2023).

Huang et al analyzed non-invasive thermometers for continuous measurement of the temperature of body cavities (Deep body temperature) in everyday medical practice. A thermometer based on the dual heat flux method (T_DHFM) and an ear canal thermistor (ACT) were used in two studies focusing on the prevention of heat stroke in high temperature and humidity conditions, as well as temperature monitoring in patients with spinal cord injuries. The CoreTemp medical device, based on the zero heat flux method, was also used as a reference for

DBT. Throughout these studies, the availability and performance of each thermometer have been discussed, highlighting the importance of selecting an appropriate method for measuring DBT (Huang et al, 2016).

3. Explanation for tracking time

It is expected that a patient with an infection or some other condition that causes fever during the 8 hours of monitoring has at least one febrile episode. Subsequent monitoring of the effects on the skin from 24h and 72h are explained by the fact that any allergic reaction on the skin will be present in 24 hours, and a late reaction maximum after 72 hours. If there is a reaction after 72 hours from the end of the study, the researcher is obliged to investigate in detail the reasons for the possible reaction.

4. Explanation for the selected study population

The system for continuous telemonitoring is intended to be used on children under 6 years of age, primarily babies or younger children, so the selection of patients of this age is crucial for testing.

Ensuring participant safety is the primary objective of this investigation. The adult cohort offers a significant advantage in this regard, as it allows for comprehensive clinical assessments, including direct subject examination, skin inspection, and structured interviews procedures that are inherently more feasible and informative when performed with cooperative adult participants. Adults are better able to articulate their experiences and provide meaningful feedback regarding device comfort, usability, and potential side effects. For this reason, the adult population was selected for this phase of the study, as it enables more effective collaboration with the clinical research team and ensures a robust foundation for future pediatric trails.

6. RISKS AND BENEFITS

1. Expected benefit

The Baby FM system for continuous body temperature measurement is intended for measuring the body temperature of the babies and the small children. In order to minimize the risk to this population, the device is first being tested on adults. The reasons for conducting a clinical trial on adults are as follows:

- Identification of any unforeseen risk
- Assessment of anticipated risks and their solutions
- Facilitation of effective communication with clinical trial participants

There is no direct benefit that the participants in this clinical trial will have, except that based on their positive experience, the next clinical trial, in children, will be able to be conducted. A potential benefit in the future, should the device be registered, for subjects in this clinical trial is that they too will be able to use this device to measure their own temperature, as the device has no age limit for use.

Furthermore, participants involved in this phase of the clinical trial contribute to advancing pediatric care, as the development of accurate and continuous real-time temperature monitoring may enhance infant safety and provide parents with greater reassurance and uninterrupted rest.

2. Expected side effects of the device

The only anticipated adverse effect in this clinical trial is localized skin irritation at the site of device application. However, the likelihood of such a reaction is considered minimal, given the use of a textile strap composed primarily of cotton with a low proportion of elastane materials generally well tolerated by the skin. Moreover, the device casing is coated with medical-grade silicone, which serves to further minimize the risk of dermatological irritation. Finally, the contact sensor, positioned in the armpit is constructed from biocompatible metal and should not anticipated to elicit any dermatological adverse effects.

The sensor is connected to the phone using Bluetooth Low Energy technology, which is known for its very low risk and is embedded in existing devices that we use every day. The level of Bluetooth radiation has already been tested and showed low values, which are normally used in commercial applications.

No serious side effects of the device are expected. Studies on similar technologies have shown that there are no serious adverse events during the testing and use of the similar medical devices.

3. Residual risks associated with the medical device

The remaining risks associated with the medical device are described in the Protocol, section 6.7 and the Investigator Brochure, chapter "Risk Management" and in the document Risks and benefits.

4. Risks associated with participation in a clinical trial

During the use of the investigated medicinal product, the subjects may have reactions on the skin in the form of itching, redness, pain, or some other symptom or sign at the point of contact between the medicinal product and the skin. It is possible that the subjects have a feeling of anxiety and discomfort due to wearing the tested product. Allergic reactions are possible in people who are allergic to the materials from which the medical device is made. Although there are risks, it is estimated that the probability of occurrence of some of the mentioned events is low, and if the event occurs, the solution will be in accordance with the Protocol.

5. Possible interactions with concomitant medical treatment

Baby FM medical product is not considered to interact with any medication. The only potential interaction of the Baby FM medical device could be with implanted pacemakers or other devices on the skin or implanted in the body that emit electromagnetic radiation, but subjects with implanted pacemakers or other devices that emit electromagnetic radiation will not be included in this clinical trial.

6. Steps to be taken to control or mitigate the risk

According to the sponsor, this medical device represents a device with a low risk to the health of the subject. However, this is a study, the first on humans, so in this regard, there is the possibility of unforeseen risks.

If unexpected risks to the subject's health occur, the sponsor will consider the relevant clinical data, information about the device and the need for improvement of the device before exposing the next subject in the trial.

Clinical trial participants will be observed by qualified clinicians during and after use of the investigational product and, if necessary, provided by adequate care and treatment.

The risk of allergic reactions is reduced by careful studying the anamnesis of each subject during screening. Subjects who are allergic to any material from which the test device is made will not be included in this test.

If there is a febrile convulsion or any other complication of the underlying disease, a sudden worsening of the health condition due to the underlying disease, or any systemic reaction during the temperature measurement, the tested medical device will be removed from the subject and stopped further participation. The medical assistance will be provided to the participants and will be monitored until the condition stabilizes. Given that the respondents have already been hospitalized, any emergency assistance will be immediately available to the participants if needed. If additional emergency care or resources are required, the subject will be provided with emergency care and transport to a different level (or specialty) hospital if necessary.

Most adverse events that are expected and that might occur can be managed in the trial clinic by the trial team.

Privacy risks are mitigated by using unique identification numbers instead of participant names, limiting access to clinical trial information, and not using participant names or identification in any publication. Each entity involved in the implementation of this clinical trial must respect the confidentiality of the subjects in accordance with all applicable laws and regulations, including the Law on Personal Data Protection, Official Gazette of the Republic of Serbia no. 87/2018.

7. Risk and benefit rationale

Table 2 shows a list of all components with potential risks, an explanation of the risks and a potential solution.

Table 2. Risks, rationale and potential solutions to risks

Component	Risk	Risk Assessment	Assessment Reasoning	Solution
Bluenrg-m2sp	Radio frequency radiation	3	As a communication device that functions via bluetooth protocol at a frequency of 2.4Ghz, the device emits radio waves at very low powers.	The device works at very low power, with certificates from verified laboratories and telecommunication agencies that guarantee operation at power far lower than the predefined maximums. The device has certification (FCC) which guarantees that it cannot produce intentional or unintentional radiation that can disturb the operation of other devices.
TMP117	Poor chip calibration	1	Overheating (300C+) during the manufacturing of the device can disrupt the calibration	When manufacturing the device, the construction protocols are followed, which minimizes the probability of damage.
CR2023	Ingestion, mercury, cadmium, leakage	4	The battery is small and children may accidentally or intentionally swallow the battery, which can lead to serious injuries and burns in the esophagus and stomach. Batteries can contain traces of heavy metals, which creates a problem with long-term disposal. Improper storage of the battery can lead to leakage.	The battery that is going to be used is high quality. The manufacturer guarantees quality with accompanying certificates. For the purposes of the clinical study, batteries which will be used have the manufacturer guarantees that they do not contain heavy metals. The battery is secured with a cap and screw that reduces the likelihood of swallowing to a minimum.
Flex Cabl	Flex cable break	2	A thin flexible strip connects the device and the sensor board. Improper and rough handling of the device can break this connection. In this case, the device reports an error and stops works.	The device contains a protocol that reports the loss of connection with the sensor, in which case it reports an error to the monitoring device (phone).
Printed board	Possible mechanical injuries, possible presence of lead in traces	0	Depending on the assembly techniques, the material used to make the components contains traces of fiberglass, lead and heavy metals.	The device is manufactured according to the latest standards, and the presence of heavy metals is eliminated from this component. The security component is in the housing, and the contact with the user minimizes.
Battery holder	A poorly fixed or loose holder can lead to turning off the device	1	Rough handling of the battery holder can lead to a loose of connection which can disrupt the device's power supply.	The device comes with accompanying instructions that minimize the chance of damage when replacing the battery.
Mechanical switch	Unintentional device shutdown	1	The mechanical switch is located on the device panel. Switching switch causes the device to shut down.	The mechanical switch is in the case, so it is impossible to access it without intentionally removing the cover.
Voltage Regulator	Brownout (turning off the device in the middle of a low voltage)	1	Powering with an empty battery can cause the device to shut down	The device contains an integrated circuit for battery monitoring. In the event of a voltage drop, it reports an error.
LED Diodes	The indicator light can cause problems in epileptics	2	No risk	During the duration of the study, the diodes will be switched off. Accompanying warnings are attached to the device. There is an option to keep the diodes off permanently.

1-minimum risk 10-maximum risk (assessed by the Baby FM team)

As shown in Table 2, there are minimal health risks, but they can also be overcome. The highest risk is swallowing the battery (for small children), but the solution is certainly to secure the battery in a separate compartment and close it with a screw.

A slightly lower risk is radiofrequency radiation, but it is minimized, either with low power, or with a frequency that is controlled by the current temperature reading (in a stable afebrile or subfebrile conditions, the sensor sends a temperature report only occasionally, at certain intervals).

The thin flexible band can break, but any damage to the device is resolved by notifying the user through the app that there is a malfunction and that the device's functioning is no longer valid.

The other risks are negligible, but each has a potential solution attached.

7. OBJECTIVES AND HYPOTHESES OF THE TEST

This study has primary and secondary objectives.

1. Primary and secondary goals

The primary objectives of the study are:

- Efficiency - accuracy of the body temperature measurements in the adults.
- Safety - absence of a side effects on the patient's skin due to contact with the sensor and/or accessory cotton fabrics with silver threads
- Performance of the device - adequacy of the system functioning (connection with the phone, temperature measurement, continuity of the connection, adequacy of the software)

The secondary objectives of the study are:

- Participant's comfort during the sensor usage
- Level of anxiety due to constant measurement of the body temperature and wearing sensors on the body

2. Hypotheses

The assumption of the study is that the correlation of measurements of two devices is 0.8 or more (working hypothesis) against the assumption that the correlation of measurements of two devices is less than 0.8 (null hypothesis).

Based on the above, this study tests the following hypotheses:

H0: $r<0.8$

H1: $r\geq0.8$

To test this hypothesis, a 95% confidence interval for the strength of association (Pearson's correlation coefficient) will be calculated with a precision of 0.075. This will confirm that there is a strong correlation between the two methods of measuring body temperature (in the literature, an extremely strong correlation of 0.8 and above is considered).

3. Claims and performance of the medicinal product to be verified

During the proposed clinical trial, the following performance of the BABY FM medical device should be checked:

- temperature measurement: whether the tested medical device BABY FM measures body temperature and whether it works in real life conditions
- connection with the phone (connection, connection stability, connection interruptions)

- continuity of connection: whether if one or more disconnections between the tested BABY FM medical device and the mobile phone
- adequacy of the software: does the software alert the user when the temperature increases above prespecified threshold, and whether the software adequately informs the user about the drug dosing.

8. STUDY DESIGN

1. General

1. Brief description of the study

This study is a single-center, non-randomized, exploratory, diagnostic study with one study group. Subjects who are hospitalized due to any type of infection or any other disease that results in fluctuating body temperature (increase, decrease) will be included in the study according to the criteria for enrollment in the study. Each subject who will be included in the clinical trial will have their body temperature measured with the tested telemedicine system for continuous body temperature measurement (Baby FM) and a standard, gallium thermometer.

Based on the existing data on the respondents in the Clinic department, the researcher will select those respondents who meet the criteria for the enrollment in the study. After the selection of the respondents, the researcher will explain in detail to the respondents about the study objectives and the design of the study. The researcher will especially draw attention to the potential side effects of the system, which are mostly related to the possible skin irritation. Also, the researcher must explain that it is a Bluetooth technology of the data transmission from the sensor to the mobile phone and that it has not been shown to have a harmful effect on the morphology and function of the organs, but every situation will be recorded and investigated.

If the subject voluntarily decides to participate in the clinical trial, he/she must confirm this by signing Informed consent form.

After agreeing to participate in the study, patients can be eligible to participate for a continuous temperature measurement.

Before placing the device, the principal investigator/co-investigator takes a picture of the subject, but only where the sensor will be placed. The purpose of taking photos is to determine if there have been changes in the skin after wearing the device.

The subject is instructed to monitor whether the device is in the correct position and, if any movement occurs, to call a member of the research team to check technical details related to the sensor. The subject is not obliged to measure the temperature, but if he is willing, he observes the adequacy of the sensor localization and informs a member of the research team of any deviation from the intended localization. The second obligation of the respondent is to fill out a questionnaire on satisfaction with the use of the medical device, which is completed when the device is removed.

The principal investigator/co-investigator checks the device, parts of the device and connects the device to a mobile phone located in the same room as the patient at a distance of no more than 3 meters.

Once the principal investigator/co-investigator confirms that the system setup is adequate, the measurement can begin. The tested device starts measuring temperature, as soon as it is set up, and the temperature measurement is done automatically every 10 seconds, but can

be changed to 30-60 seconds, if necessary. At the same time, manual temperature measurement, which is done by the researcher, begins. It is not expected that these two temperatures completely agree, especially on the first measurement if the continuous measurement system was in a cold room or other places where the temperature is different from the hospital room temperature.

Each subsequent manual measurement is done for 30-60 minutes. If the measurement starts at 8:00 a.m., the scheduled measurements are at: 8:30, 9:00, 9:30, 10:00, 10:30, 11:00, 11:30, 12:00, 12:30, 13:00, 13:30, 14:00, 14:30, 15:00, 15:30, 16:00. At the moment when the patient's temperature starts to rise, the frequency of manual measurement is switched from 30-60 minutes to 15-30 minutes. If the subject is given an antipyretic drug, until the temperature drops, the manual measurement are on 15-30 minutes, and then returns to the usual interval of 30-60 minutes. The measurement with the tested device lasts all the time and continuously every 10 seconds, but it can be changed to 30-60 seconds.

If a febrile convulsion or any other complication of the underlying disease occurs during the measurement, the tested device is removed from the participant and he stops further participation.

The measurement with the tested device is stopped no later than 72 hours after the installation of the device. The device is removed and the skin is inspected. The patient is interviewed and any changes on the skin are recorded. In addition, any other symptoms that are not necessarily related to the tested system are recorded.

When the measurement with the test device is completed (up to 72 hours from the start of the subject's participation), the device is removed, and a member of the research team takes a picture of the place where the sensor was positioned.

After the last measurement, a member of the research team re-examines the patient's skin and takes a picture of the place on the skin where the device was. The patient is given instructions to pay attention to changes in the skin within 72 hours and if there are any changes, to take pictures of them and send them to the researcher if he is not at the clinic. If the subject is still at the clinic, the researcher takes a picture of the place where the tested device was positioned.

2. Measures to avoid bias

This is a non-randomized clinical trial with one group of subjects. This clinical trial is not randomized or blinded trial. Each subject included in this clinical trial will have their body temperature measured with the test medical device Baby FM and a comparator (gallium thermometer).

3. Primary and secondary outcomes

The primary outcomes are:

- efficiency

The measure of the efficiency is the agreement between the temperature measured by the telemedicine system and the standard gallium thermometer – based on this explanation.

Efficacy will be assessed by evaluating whether the use of the telemedicine system leads to earlier detection and management of febrile episodes, reduced febrile duration, and improved clinical decision-making compared to standard care.

- measurement accuracy

Agreement will be evaluated using appropriate statistical methods (e.g., Bland–Altman analysis or intraclass correlation coefficient), to assess the precision and reliability of the telemonitoring system.

- safety

Safety will be assessed by monitoring, documentation, and classification of all adverse events and device deficiencies potentially related to device use - during maximum 72 hours while wearing the device and during 72 hours from the moment of removing the tested device. Particular focus will be placed on dermatological reactions, thermal discomfort, device malfunctions that may result in clinical misinterpretation. Events will be assessed for seriousness, severity, causality, and expectedness.

- system performance

Performance is measured by frequency of the system interruptions, system crashes, system errors.

System performance will be evaluated by examining the operational capabilities of the telemonitoring device under standard usage conditions. Performance indicators will include data acquisition frequency, real-time responsiveness, sensor accuracy, and the system's ability to consistently record and display temperature values without delay. Additional parameters such as the efficiency of Bluetooth communication, synchronization between the device and the mobile application, and the quality of temperature data visualization will also be assessed. These measures will collectively determine the system's functional adequacy for continuous physiological monitoring.

- system reliability

System reliability refers to the stability and consistency of the device's operation over time. It will be assessed by monitoring the frequency, duration, and nature of any technical failures or interruptions during use. This includes system crashes, signal loss, hardware malfunctions, and software errors. The ability of the system to maintain uninterrupted temperature monitoring for the full duration of use (up to 72 hours) will serve as a key indicator of its reliability. Furthermore, the system's resilience to environmental conditions (e.g., humidity, body movement, wireless interference) will be taken into account. A high level of reliability is essential to ensure valid data collection and user confidence.

Secondary outcomes are:

- Respondents experience related to the system usage

Measures of respondent's experience related to the system are:

- Anxiety level during a febrile episode with a telemedicine system for continuous body temperature measurement
- The comfort level while the respondent is wearing the system

4. Methods and time for assessment, recording and data analysis

Body temperatures will be recorded using two methods, test (Baby FM) and reference (gallium thermometer). The measurement time with the test tool is up to 72 hours, continuously, while the measurement time with the reference tool is between 30 and 60 minutes, depending on the temperature trend. Measurements using the reference method are recorded in a paper clinical report form (CRF), while the test is recorded in the database, directly in the device (application).

5. Respondent replacement

Subjects who have elevated body temperature are planned to be participants in the study. If the patient becomes afebrile during the study, it is recommended that he/she should be replaced by a new patient who is likely to have a febrile episode during follow-up. For the quality of the results, it is necessary that at least half of the patients have a febrile episode during the study.

2. Tested medicinal product and comparator

1. Description of investigated medicinal product and comparator usage

After signing the Informed Consent Form, performed screening procedures and determined that the subject meets the criteria for inclusion in the clinical trial, the subject will be given

the Baby FM investigational medical device. A member of the trial team will check if the device setting is adequate, connect the trial medical device to a mobile phone and begin automatic, continuous body temperature measurement with the test medical device every 10 seconds (with a possible change to 30-60). Each subject is expected to wear the tested medical device for up to 72 hours, but the tested medical device will be removed every 8 hours, and a member of the testing team will check the place where the medical device was positioned. If there are no changes on the skin, discomfort, symptoms and signs that may be associated with the device (itching, redness, or some other symptom or sign), the device will be returned, and the measurement will be continued. The measurement with the tested device will be stopped no later than 72 hours after the device has been installed. The device will be removed, and the skin will be inspected. The subject will be interviewed and any changes on the skin will be recorded. In addition, any other symptoms that are not necessarily related to the tested system will be recorded, and the subject will fill out a questionnaire about the experience related to wearing the sensor (Questionnaire for the subject).

From the moment when the measurement of the body temperature has begun with the tested medical device, the subject's body temperature will also be measured with a standard gallium thermometer (comparator) in the opposite armpit. It is planned that the measurement of body temperature with a comparator is carried out in a time interval of 8 hours every 30-60 minutes. If the measurement were to start at 8:00 a.m., the predicted measurements with the comparator are at: 8:30, 9:00, 9:30, 10:00, 10:30, 11:00, 11:30,
12:00, 12:30, 13:00, 13:30, 14:00, 14:30, 15:00, 15:30, 16:00. When the subject's temperature starts to increase, the frequency of measuring with the comparator will be switched from 30-60 minutes to 15-30 minutes. If the subject is given an antipyretic, until the temperature drops, the measurement with the comparator will be performed for 15-30 minutes and then return to the usual interval of 30-60 minutes. If the subject still has a febrile episode after the eight-hour interval of measurement with the comparator, monitoring continues until the temperature drops to normal 1 hour more.

If a febrile convulsion or any other complication of the underlying disease occurs during the measurement of body temperature, the tested medical device will be removed from the subject and he/she will stop further participation but will be monitored until the condition stabilizes.

2. Justification of the choice of comparator

A clinical thermometer without mercury – gallium thermometer, Model CRW-1108, registered by ALIMS on 26-1-2017, reference number 515-02-03038-16-001, was chosen as a comparator in the clinical study. The gallium thermometer was chosen because Baby FM imitates the measurement of body temperature in an old fashion method, in the armpit, all with the aim of digitizing the temperature values that were once measured with a mercury thermometer. Since mercury thermometers are retired, gallium thermometers are used in this study.

3. Other medical devices or drugs that will be used during the clinical trial

Apart from the tested medical device Baby FM and the gallium thermometer that will serve as a comparator, no other medical devices are intended to be used in this clinical trial. Also, apart from the therapy that every involved subject uses regularly and the antipyretics that will eventually be given to the subjects to lower their body temperature, this clinical trial does not require the use of drugs.

4. The number of investigational medicinal products that will be used in the clinical trial

The Baby FM system for continuous body temperature measurement consists of a cotton elastic band and electronics (sensors) that are placed inside a silicone thermoconductive box. Each respondent receives a cotton strip. The number of strips corresponding to the number of included subjects, i.e. 40 (personalized piece of equipment in a clinical trial), will be produced. The sensor is not personalized and there will be 5 devices at the test site, and more will be produced if necessary (if there are malfunctions, destruction of the device, loss of the device, etc.).

On the site, there will be 5 gallium thermometers, comparators (reference means), which the subjects in the study will use. It is assumed that there will be no more than 5 patients who can be in the study at the same time, so the number of the tested devices and comparators is limited to this number.

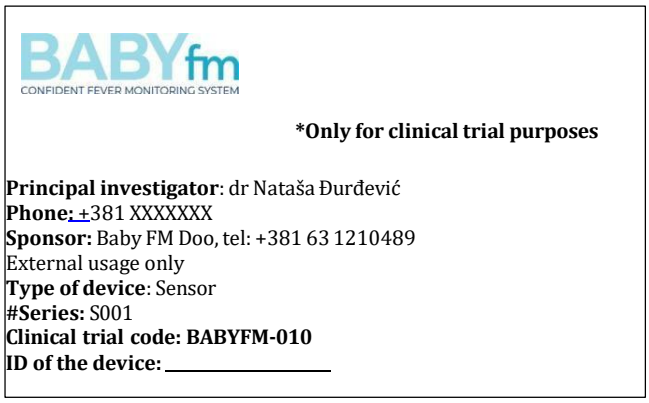
5. Maintenance and storage of the medical device

The medical device will be taken out of storage no more than 30 minutes before the start of the temperature measurement. The box with the medical device will be opened on the bed of the subject participating in the examination and taken out from the bag on the same bed.

The medical device consists of a cotton elastic band and electronics (sensors), which are specially packaged and labeled for the purposes of this study.

After sewing the tape, it is washed and then sprayed with a solution of water and alcohol. Once dry, it is placed in a ziplock bag with a label.

The label on the sensor carrier tape bag looks like this:



The devices will be sprayed with a solution of alcohol and water, then after drying they will be packed in a ziplock bag and marked with a label.



The label on the sensor pouch looks like this:

After the usage, the sensor will be sprayed with a solution of water and alcohol, then after drying it, it will be packed in a new bag and used again on the next examinee.

3. Respondents

1. Inclusion criteria

The criteria for inclusion in the study are:

- Consent to participate in the study
- A person of male or female gender
- Age 18 and over
- Possibility to measure the patient's body temperature frequently
- Persons who are hospitalized due to any type of infection or other disease that results in body temperature fluctuations (increase, decrease)
- Completed all potential diagnostics of the hospitalized patient (not interrupting the measurement of the telemedicine device)

2. Exclusion criteria

- Allergy to contact the skin with silicone, metal or cotton
- Anatomical anomalies that prevent the placement of the System
- High-risk health conditions, intensive care and the like
- A pacemaker or other device on the skin or implanted in the body that emits electromagnetic radiation

3. Criteria and procedures for withdrawing subjects or discontinuing participation

The subject can stop participating in the clinical trial at any time. Additionally, the investigator may terminate the subject's participation in the clinical trial at any time if deemed necessary. The reasons for possible termination of participation are as follows:

- Sudden deterioration of the health condition due to the underlying disease
- Any reaction on the skin during temperature measurement
- Any systemic reaction during temperature measurement
- Significant deviation from the clinical trial plan
- Technical problems related to the data collection system
- If a febrile convulsion or any other complication of the underlying disease occurs during the measurement, the system will be removed from the subject and the subject stops further participation.

If for any reason the subject is excluded or withdrawn from the clinical trial, and if the device was mounted on him, he will be monitored for the next 72 hours. If there is any possibility of health risk due to participation in the clinical trial, he/she will be examined and monitored at the clinic or by phone for the next 72 hours.

The reason for withdrawal from the clinical trial will be recorded in the CRF.

All data recorded during the follow-up of the subject, while he was in the clinical trial, or after his/her withdrawal, will be used for further analysis, unless the subject requests the opposite.

4. Recruitment of respondents

Recruitment of subjects for the proposed clinical trial will be conducted at the trial site. Participants who are eligible for participation in the clinical trial will be identified at the study site by the researcher, based on the existing data on the subjects. The researcher will select hospitalized subjects who meet the eligibility criteria for participation in the clinical trial. The expected time from the moment of the participant's recruitment to the interview with the participant about the process of informed consent is half an hour.

5. Place of examination

The proposed clinical trial is intended to be conducted at one site. If there is a change in the number of trial sites, they will be noted in the study amendments and the new version of the Protocol.

The test site where this test will be conducted is:

Pulmonology Clinic, University Clinical Center of Serbia

Pasterova 2, 11000 Belgrade, Republic of Serbia

Principal Investigator:

Dr. Nataša Đurđević, internal medicine specialist, pulmonologist Email address:

Phone number: 064XXXXXX

6. Total expected duration of the clinical trial

The anticipated duration of the clinical trial, including recruitment and follow-up, is up to 4 months. After the completion of the last recruited patient follow-up, the research site will no longer recruit subjects or follow-up subjects further. The data cleaning will be undertaken. The estimated time for data cleaning and entry into the electronic database is up to 30 days from the end of the follow-up period of the last recruited respondent.

7. Expected duration of participation of each respondent

It is envisaged that the clinical trial for each subject will last a maximum of 6 days, and that the wearing of the investigated medicinal product will last up to 72 hours (3 days), and the additional 72 hours (3 days) will be the monitoring of the possible side effects.

8. Estimated number of included respondents

This clinical trial is intended to enroll 40 adults, male or female, 18 years of age or older who are hospitalized for an illness resulting in febrile status.

9. Estimated period of inclusion of respondents

The estimated period of the predicted number of participants inclusion in the study is from 30 to 90 days.

4. Procedures

1. Procedures to which respondents are subjected

- Informed consent

The subject must personally sign and date the current version before any study procedure is applied to him.

A written version of the informed consent will be shown to the patient and each part of the document explained. This implies that the exact purpose of the study, the benefit for patients and possible risks and side effects that may occur during or after the study will be explained in detail to the study participant. Also, the researcher must explain that a Bluetooth technology of data transmission from the sensor to the mobile phone is used, and that it has not been shown to have a harmful effect on the morphology and function of the organs, but every situation will be recorded and investigated.

It will be clearly and decisively explained to the patient that he/she can withdraw from the study at any time without any explanation or consequences for his/her treatment.

The patient will be given as much time as he wants to think about participating in the study, as well as the possibility to ask the researcher at any time about any ambiguities related to the study.

The signed and dated informed consent will be made in two copies, one for the study participant and the other to be kept at the study site. The researcher who conducts the interview regarding the process of obtaining the informed consent of the subject must be sufficiently qualified and trained to know everything about the study, as well as to be authorized by the principal investigator to obtain consent from the patient.

Screening

Screening of patients is performed in the clinic. The researcher will have insight into the current attendance of patients who have febrile conditions, and according to his assessment, possible participants will be screened.

After identifying potential participants, a patient interview will be conducted including an explanation of the study to the patient and signing of the informed consent (see section 8.4.1 for details). If the subject voluntarily consents and confirms by signing the Informed Consent Form, the researcher checks the adequacy of the subject to enter the study through the inclusion and exclusion criteria (see section 8.3.1 and 8.3.2 for details).

Patient screening includes the following patient details:

- Demographics - date of birth, sex

Data on date of birth and gender will be taken during the interview with the patient.

- Previous illnesses and allergic conditions

Anamnesis related to previous diseases as well as allergic conditions and reactions and changes on the skin will be taken from the patient.

Physical examination

The physical examination includes an examination of the patient's skin where the sensor will be placed, as well as other parts of the chest and the skin of the hand (for possible allergic reactions that spread from the place where the sensor is placed). The part of the skin where the sensor will be placed will be photographed by the researcher, and the photo will be marked with the identification number of the subject and the date and time of the photo taken.

Medications the participant is currently taking

All medications the patient is currently taking will be recorded, including supplements and vitamins.

Study procedures

Before placing the device, the principal investigator/co-investigator takes a picture of the subject, i.e. the place where the sensor will be placed. The purpose of taking photos is to determine if there have been changes in the skin after wearing the device.

The device is placed on the subject immediately at the beginning, and after verifying that everything is in place and functioning, the body temperature measurement begins. In parallel, the subject's body temperature will be measured with a standard gallium thermometer in the opposite armpit.

The subject is instructed to ask if he/she is able to monitor whether the device is in the correct position and if any movement occurs, to call a member of the research team to check the technical details of the sensor. The subject is not obliged to measure the temperature, and observing the adequacy of sensor localization is on a voluntary basis.

The principal investigator/co-investigator checks the device and the parts of the device and connects the device to the mobile phone located in the same room where the respondent is at a distance no more than 3 meters.

It is planned that the measurement will start on the full hour and that all measurements will be performed every 30-60 minutes, until the moment of temperature increase, when the measurement frequency will change to 15-30 minutes. After the temperature decrease, the measurement frequency returns to 30-60 minutes.

Once the principal investigator/co-investigator confirms that the system setup is adequate, manual measurement can begin. In parallel, the measurement performed by the system is automatic, continuous, every 10 seconds, but can be changed to 30-60 seconds if necessary. The first manual measurement is performed immediately, with a gallium thermometer. It is not expected that these two temperatures completely agree, especially on the first measurement if the device was in a cold room or other places with lower temperature compared to hospital room.

Each subsequent manual measurement is done for 30-60 minutes. If the measurement were to start at 8:00, the best form for predicting the measurement is in:

8:00, 8:30,

9:00, 9:30,

10:00, 10:30,

11:00, 11:30,

12:00, 12:30,

1:00 PM, 1:30 PM,

2:00 PM, 2:30 PM,

3:00 PM, 3:30 PM,

4:00 PM … hours.

At the moment when the subject's temperature starts to increase, the measurement frequency is switched from 30-60 minutes to 15-30 minutes. If the subject is given an antipyretic, until the temperature decreases, the measurement is performed for 15-30 minutes and then returns to the usual interval of 30-60 minutes. If the subject still has a febrile episode at 16:00, monitoring continues until the temperature decreases to the normal plus 1 hour more. The measurement with the tested device lasts all the time and continuously every 10 seconds, but can be changed to 30-60 seconds if necessary.

If a febrile convulsion or any other complication of the underlying disease occurs during the measurement, the respondent's system is removed, and he/she stops further participation.

When the 8-hour measurement is completed, the device is removed and the health care provider checks the place where the sensor was positioned. If there are no changes on the skin, discomfort, symptoms and signs that may be associated with the device (itching, redness, or some other symptom or sign), the device is returned and the measurement continues according to the same principle. The measurement cycles last 8 hours, and during the breaks, an inspection of the skin where the sensor is placed and a short conversation with the subject in terms of whether he/she has any symptoms due to the device placed on his body. During the measurement, the number of breaks depends on the duration of the temperature measurement phase, and the break lasts short enough to check the condition of the skin in the place where the sensor is positioned and the condition of the surrounding skin (trunk, hands).

The measurement with the tested device will be stopped no later than 72 hours after the device has been installed. The device will be removed, and the skin will be inspected. The subject will be interviewed, and any changes of skin will be recorded. In addition, any other symptoms that are not necessarily related to the system being tested will be recorded. A member of the research team again will take a picture of the place where the sensor was positioned, and the subject will fill out a questionnaire about the experience related to wearing the sensor (Respondent Questionnaire).

Then, next is a period of monitoring the examinee that lasts 72 hours.

The subject will be instructed to pay attention to the changes of the skin within 72 hours and, if there are any changes, to take pictures of them and send them to the researcher if he/she is not at the clinic. If the subject is still at the clinic, the researcher will follow-up the subject and take a picture of the place where the tested device was positioned.

The subject can stop hospitalization during the temperature measurement phase or during the monitoring phase (after temperature measurement), but the monitoring (of 72 hours) due to possible side effects will be continued by telephone contact with the subject. In this case, the data obtained up to the time of interruption will be used for further analysis, and the subject will be contacted by phone and asked to examine in front of the mirror the place where the sensor was positioned and the surrounding skin (trunk, hands) and if he/she notices any change that was not present before entering the study, report to the clinic for further evaluation. Also, every other symptom will be reported to a member of the research team and an evaluation regarding the need to report to the clinic will be made.

If the subject is in the hospital for the entire duration of the study (which is expected for the majority of subjects who will be included in the study), the healthcare worker will monitor for 72 hours while wearing and 72 hours after removing the device (3+3 days, a total of 6 days), whether there are any changes on the skin, as well as any other symptoms. The skin examination will be performed once a day, and during the interview, the healthcare worker will ask the respondent about any symptoms and signs he/she noticed during the monitoring period.

Completion of participation in a clinical trial

The subject will be assumed as completed the study after a maximum of 144 hours, that is, 72 hours from installation of the system and 72 hours of monitoring after removing the system. The presence of symptoms and signs on the skin and the presence of other symptoms are monitored even if the subject is no longer at the clinic (via telephone).

Respondents lost to follow-up

Loss of contact with subjects must be handled in accordance with specific procedures to verify the safety of subjects and ensure that all necessary information related to the SAE will be obtained.

If during the follow-up period (72 hours after using the investigated medicinal product) the subject is not at the clinic, and the principal investigator/co-researcher documents 3 unsuccessful attempts to contact the subject, the subject will be considered "lost to follow-up". In this case, the principal investigator must contact the subject's chosen physician without delay in order to obtain information about the subject's health status.

2. Sponsor Responsibilities

Responsibilities of the Clinical Trial Sponsor include obtaining approval prior to the start of the trial, arranging for subject insurance for the clinical trial, obtaining signed contracts with the principal investigator or contract annexes with team members, reviewing significant new information related to the trial, reporting SAE, SADE, USADE to the relevant authorities, keeping copies of correspondence and data, delivering devices to the trial site, and collecting all devices from the trial site upon completion of the clinical trial. Some or all of these duties may be outsourced to third parties as needed.

As a clinical trial sponsor, BABY FM has overall responsibility for the conduct of the clinical trial, especially by ensuring that the clinical trial meets the guidelines of ICH-Good Clinical Practice (GCP), International Organization for Standardization (ISO) 14155 for clinical trials of medical devices, the Declaration of Helsinki, and all applicable national laws and regulatory requirements. Sponsor will ensure compliance with these guidelines.

All unwanted events and defects of the device will be reported by the Sponsor to the Ethics Committee of Serbia and the regulatory body.

3. Factors that may affect the outcome of a clinical trial or the interpretation of results

The measurements of the Baby FM device are directly entered into the electronic database via BLE, while the values of the gallium thermometer measurements are entered into the test sheet.

Positioning of the Baby FM device is one of the crucial factors for accurate measurement of body temperature (armpit). A possible oversight of moving the thermometer, in the sense of

going down further than the armpit, can lead to a systematic measurement error, which will be reflected in lower body temperature values than the real one.

Another possible cause of inadequate data, and thus the outcome, is a malfunction of the device, which results in an interruption of signal processing, reading values and sending values to the device that stores the data in the electronic database.

A potential risk factor for the reference method could be the insufficient measuring time of the thermometer, as it is known that gallium thermometers need a slightly more time to achieve the real body temperature, compared to the mercury thermometers.

5. Monitoring plan

The clinical trial will be closely monitored by a qualified and trained monitor. The trial monitor will periodically contact the trial site and conduct monitoring visits at the trial site. The scope and frequency of monitoring visits of the test site is described in the Monitoring Plan document. The monitoring will be carried out according to the agreed monitoring plan, and the extent of the planned verification of the original data is 100%.

The Monitoring Plan lists the BABY FM Sponsor's requirements for reporting on the progress of the clinical trial. Representatives of BABY FM or its representatives can participate in monitoring visits or independently visit the test site for adequate supervision.

- Initial visit

Prior to the start of the clinical trial, the monitor will contact the trial site to discuss the Clinical Trial Plan and data collection procedures with the trial team. The CRO will ensure that, before enrolling the participants, all essential regulatory documents, including a positive opinion from the Ethics Committee of Serbia, are available at the trial site.

- Monitoring visits during the trial period

Monitoring will be carried out according to the agreed monitoring plan. The trial monitor will periodically monitor the progress of the trial and should be given access to all necessary documents to ensure that the rights and welfare of the subjects are protected, trial data are accurate, complete and verifiable from the source documents, conduct of the trial is in accordance with the valid approved Protocol, Good Clinical Practice and all regulatory requirements.

During monitoring visits, the monitor will:

- Assess whether Informed Consent has been properly obtained from each participant
- Assess compliance with eligibility criteria (criteria for inclusion/exclusion of participants) of the Protocol
- Check the regularity of conducting and documenting the clinical trial
- Check the liability for the medical device

- Check the accuracy and completeness of filling out the CRF, original documentation and other records related to the clinical trial
- Review documentation of safety assessments required by the Protocol, including SAEs.
- Ensure the existence of documentation on the withdrawal and death of the respondent, with the stated reasons.

The principal investigator agrees to allow the monitor direct access to all relevant documents, including access to the subject's medical records, and to set aside time to discuss all relevant matters with the monitor. Also, the principal investigator agrees that other members of the trial team should take time to discuss all relevant issues with the monitor.

The Principal Investigator agrees to allow representatives of BABY FM or its representatives to occasionally attend monitoring visits or to visit the study site independently.

- Final visit

Upon completion of the clinical trial, the clinical trial monitor and principal investigator will conduct the following activities:

- Clarification and/or resolution of queries
- Check records, reconciliation and return of used medical devices to the Sponsor
- Review the completeness of data and documentation
- Ensure that clinical trial data are handled in accordance with the sponsor's instructions

9. STATISTICAL DATA PROCESSING

1. Description of statistical methods

Descriptive statistical methods will be used in this study.

- Absolute and relative numbers (n, %) will be used for attributive variables.
- For numeric variables, the following will be used: measures of central tendency (arithmetic mean, median) and measures of dispersion (standard deviation, interquartile range, interval of variation).

All descriptive parameters will be presented with 95% confidence intervals.

The diagnostic accuracy of the device will be tested by analyzing the agreement of the two methods.

Absolute values of temperature will be tested by correlation analysis (Pearson correlation) and by interclass correlation (ICC).

Graphically, the agreement of absolute values will be shown using a scatter diagram or by Bland-Altman diagram.

2. Sample size

This is a pilot study, exploratory in nature, the first on humans. The sample size was determined based on the sample size calculation formula. The sample size was set based on the recommendations of the existing guidelines (FDA, EMA), but taking into account that it is a low-risk non-invasive diagnostic method, 40 respondents were expected to participate in the study.

The primary objective is to examine the agreement between the two methods (effectiveness).

A strong correlation (depending on the author) is considered to be between 0.6 and 0.8, while extremely strong is over 0.8. In case of agreement between these two methods (gallium thermometer and Baby FM), a correlation of 0.9 is expected. A sample of 32 subjects is sufficient to estimate a 95% confidence interval (two-tailed) for a correlation level of 0.9 and an interval width of 0.15 (precision of 0.075). In order to take into account possible interruptions of the study, withdrawal of patients and similar, additionaly 8 subjects will be included in the study, resulting the total number of 40 subjects

3. Significance level

In this study, the agreement of the two methods will be tested using Pearson's correlation analysis and the interclass correlation coefficient. All p values less than 0.05 will be considered as values to reject the null hypothesis.

All results will be presented using as point estimate and 95% confidence interval for the point estimate.

4. Missing data

No replacement of missing data is planned. All data where one or both measurements of reference or test devices will not be taken for further analysis.

5. Patient populations and subpopulations

All patients whom at least one measurement is performed will be considered the study population to assess efficacy (Efficacy Population, EP population).

All patients on whom the system was placed, regardless of whether the measurement was performed, will be considered the population to assess safety (Safety population, SAF population).

6. Interim analysis

An interim analysis is not planned for this study.

7. Deviations from the statistical plan

Any deviation from the statistical plan will be recorded in the statistical report. The deviation will be explained as follows:

- Deviation number
- Deviation description
- Reason for deviation
- The influence of deviation on the statistical conclusions.

8. Analysis of special groups of subjects (populations)

In this study, it was planned to analyze two populations. For device security purposes, SAF population will be analyzed, while the EP population is planned to be analyzed for the effectiveness test.

No other populations are planned in this trial.

10. DATA HANDLING

The principal investigator is required to ensure the accuracy and completeness of the data, while data collection is the responsibility of the principal investigator and co-investigators. The collection of the data must be in time frames that allow a timely review of the data to detect security risks for the subject. The CRO will be responsible for activities related to data management, including data quality analysis and presentation of the final version of the database.

1. Test sheet for collecting data about the respondent

Data collection will be performed using a paper Clinical Report Form (CRF). Trial team members will enter all clinical data directly from the source documents into the CRF. For each participant, a CRF must be completed and signed by the principal investigator. If a participant withdraws from the study, the reason must be stated in the CRF. If a participant is withdrawn from the study due to an adverse event, the outcome must be clearly documented.

The researcher should ensure that all data entered in the CRF are accurate, complete and entered on time. The Principal Investigator will maintain all information in the CRFs and all source documents relating to the data collected from each participant. CRFs should be completed by the principal investigator as soon as possible after all information are collected.

CRFs along with essential documents will be stored in accordance with the requirements of the regulatory authorities.

All CRFs will be verified for accuracy by the study monitor. Monitoring will be performed as a complete data review. Each CRF will be associated with a study participant ID number. Name and other identifying information will not be included in any document other than the original clinical documents which remain at the clinic in a safe place. Anonymized data will be transferred to an electronic database, in a spreadsheet. The verified database will be locked, and the password will be set by the CRO and signed by the person responsible in the CRO.

Data on measurements with a standard thermometer will be entered in the Test sheet, while data from the device being tested will be stored on the device connected to the sensor and which is part of the system.

All data will eventually be transferred to the electronic database in Spreadsheet format and will continue as such prepared for data processing.

The researcher undertakes to keep all data collected at the clinic in a safe place in accordance with the law for 15 years after the end of the study.

2. Source documents

Source documents serve to provide evidence of the existence of the subjects who participated in the study, on whom the measurements were made, and the data that will be used for further processing.

All original documents will be exclusively kept at the clinic where the examination is performed.

All original documents or signed photocopies of the patient documents from the clinic will be considered as original data from the clinic.

Prior to study start, the sponsor determines which documents or data entry fields by the research team will be considered source documents. The source documents include anamnestic data about the patient, namely demographic data (gender, age), data related to the patient's diagnosis, data related to the therapy the subject receives, and anamnestic data related to previous illnesses and allergies. In addition to these, the source documents include a questionnaire for the respondent and a table with recorded values of the temperature measured with a gallium thermometer by the researcher.

All documentation will be stored at the clinic in a safe place, in a cabinet with a key, and the researcher will be responsible for that data.

The transfer of the data to the electronic database will be performed by anonymizing the patients and further handling of the data by statisticians will be exclusively with anonymized data.

3. Data management

All CRFs, reviewed and verified by the monitor, will be sent to the Sponsor. All data management activities will be performed in accordance with Standard Operating Procedures (SOP). Procedures for reviewing the data, cleaning the database, issuing and resolving data inquiries are detailed described in Sponsor's data management plan document.

4. Confidentiality

All data and information collected during this clinical trial will be treated as confidential by the Sponsor. However, regulatory authorities will be allowed full access of the records. All data used in the analysis of this clinical trial will be anonymous and the names of the subjects will not be used.

11. AMENDMENTS TO THE PROTOCOL

All changes and additions to the Protocol will be adequately recorded and reported to the Agency and the Ethical board of Serbia. For better visibility, the changes will be tabulated in the form:

- Page number where the change is made
- Section of the Protocol where the change was made
- Original text
- Modified text
- If the Protocol is supplemented with a completely new text, then it will be entered in the table (but items 2 and 3).

12. DEVIATION FROM THE PROTOCOL

Deviation from the Protocol is any non-compliance with the Protocol, good clinical practice or any regulatory or ethical requirement. Non-compliance can be caused by the participant, the researcher or a member of the trial team. As a result of any deviations, corrective measures need to be developed and implemented in a timely manner. Study procedures will not be changed without the consent of BabyFM DOO. Minor deviations of the Clinical Trial Plan will be analyzed individually, taking into account all information related to the reason of the deviation.

It is the PI responsibility to promptly, upon identification, report deviations to the sponsor. If necessary, reports of the deviations from the Protocol must be sent to the Ethics Committee of Serbia and the regulatory body.

To limit the possibility of deviations from the Protocol, the Principal Investigator and trial team members will be trained (and retrained, as necessary) to implement the Protocol.

1. Statement of Deviation from the Clinical Trial Plan

The investigator will seek permission from the Sponsor, the Ethics Committee of Serbia and the regulatory body for any intention to deviate from the Protocol. Under no circumstances researcher must not deviate from the Plan without the prior approval of the Sponsor, the Ethics Committee of Serbia and the regulatory body.

In extraordinary circumstances, deviations from the Protocol in order to protect the rights, safety and well-being of the subjects may be carried out without the prior approval of the Sponsor, the Ethics Committee of Serbia and the regulatory body. In that case, the deviation from the Protocol will be documented and reported to the Sponsor, the Ethics Committee of Serbia and the regulatory body as soon as possible, but no later than five (5) working days after the emergency occurred.

All deviations will be documented in the CRF.

2. Recording, reporting and analysis of CIP deviations

Any protocol deviations will be recorded at the clinic. Any deviation will be recorded with the following characteristics:

- Deviation number (in order)
- Deviation description
- Assessment of the impact on the outcome of the study
- A possible solution for the deviation
- Does the patient drop out of the study due to deviation and/or change population (EP/SAF)
- Significant protocol deviations that affect the outcome of the study will be reported through a report to ALIMS and Ethical Serbian committee.

3. Notification Requirements and Timeframes

If minor deviations of the Protocol are registered, they will be reported to ALIMS and the Ethics Committee of Serbia in a period of 3 months or more often. Significant deviations, which are estimated to have a serious impact on the outcome of the study and on the safety of the subjects, will be reported to ALIMS and the Ethics Committee of Serbia as soon as it is established that a deviation has been made. The person in charge of the application is Prof. Dr. Ivan Soldatović.

4. Corrective and preventive measures and criteria for disqualification of the principal researcher

Preventive measures consist of the training of the principal investigator by the sponsor, in order to carry out each procedure in an adequate manner, prescribed by the study protocol. The sponsor will inform the principal investigator of all possible measures if the principal investigator behaves unethically and unprofessionally and not in accordance with the study protocol.

The principal investigator may be disqualified from the study if:

- It does not adhere to the protocol, good clinical practice and all requirements of the applicable laws of the Republic of Serbia
- Knowingly and/or intentionally influences the results of the test
- Incorrectly enters and processes the data that is collected
- He/she behaves unethically and unprofessionally
- It does not protect the rights, safety and well-being of data subjects.

13. RECORD OF USE OF MEDICINE DURING A CLINICAL TRIAL

The medical device will be stored in a secure location at the test site, in a lockable access-controlled room. At the start of the clinical trial, the Principal Investigator or a member of the trial team (delegated by the Principal Investigator to be responsible for the medical device) will record all necessary information regarding the delivery of the medical device to the trial site by the Sponsor. During the duration of the test, the team member will keep records and track the medical device (carrying tape and sensors) at the test site, check the number of returned used medical devices by the examinee. Upon completion of the clinical trial, or by the Sponsor's request, the principal investigator will return all investigational medicinal products to the Sponsor. The sponsor’s standard operating procedures will be applied for the transportation, receipt, storage and return of the medical product. In the case of damage or malfunction, the medical devices must not be used, and the principal investigator or a qualified member of the trial team must contact the Sponsor for further instructions.

14. DECLARATION OF CONFORMITY

1. Ethical principles

The study will be conducted in accordance with the applicable regulatory requirements of the Republic of Serbia, the ethical principles derived from the Declaration of Helsinki and the Good Clinical Practice Guidelines, all in order to ensure the highest possible protection of study participants (respondents). If EOS or ALIMS have additional requirements related to the conduct of the trial, the requirements will be met according to the instructions of these two bodies.

2. Financing and insurance

Sponsor Baby FM DOO, Veljka Dugoševića 54, 11000 Belgrade finances this clinical study. The sponsor will provide additional financial assistance in the purchase of equipment, technical support and financial assistance for the publication of the results. Also, the sponsor will bear other costs related to the application of the study (costs of opinions of the Ethics Committee of Serbia, submission of documentation to ALIMS), as well as insurance of the respondents.

Any financial agreement with the clinic where the examination is performed will be regulated by a separate document.

Baby FM DOO, Veljka Dugoševića 54, Belgrade, will provide insurance for participants in the study in case of the need for any additional treatment for events related to the study device being tested.

Before the start of the study, the sponsor provides insurance for the 40 subjects who are expected to participate in the study.

3. Provision of emergency medical assistance and assistance due to the occurrence of other adverse events

Study participants will be observed by qualified clinicians during and after use of the investigational medicinal product. Considering that the participants in the study (respondents) are already hospitalized, any emergency assistance will be immediately available to the participants if needed. If additional emergency care or resources are required the participant will be provided with emergency care and transport to a second- level hospital (or other specialty) if necessary.

Most of the adverse events that are expected to occur can be treated in the clinic where the trial is being conducted by the clinic staff and have no cost to the study participant.

4. Declaration of Helsinki

The researcher will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

5. Good clinical practice guidelines

The investigator will ensure that this study is conducted in full compliance with all regulations and guidelines of good clinical practice in clinical trials, ie the standard for clinical trials of medicinal products in humans (ISO 14155).

6. Approval of the study by the Ethics Committee

No activity related to the study will begin before the Protocol and other supporting documents have been reviewed and given a positive opinion by the Ethics Committee of Serbia. Potential amendments during the study will also be reviewed and approved by the same body.

After obtaining permission from the Ethics Committee of Serbia, the study, which was also reported to the Agency for Medicines and Medical Devices, as well as other instances, begins with the initiation of the clinic, after announcing that the application procedure has been successfully completed.

The principal researcher is also obliged to report all problems related to the study to the Ethics Committee of Serbia, especially risks related to patients, all in accordance with the rules of the board.

The principal investigator may not change the Protocol or any procedure before the written approval of the Ethics Committee of Serbia, except in the case of immediate danger to the subject or when the changes are made for logistical or administrative issues (change of telephone, address, etc.).

BabyFM doo will report to ALIMS and the Ethics Committee of Serbia any information related to testing the device and possible endangerment of patient safety, as well as the risk/benefit ratio for participation in the study.

The Principal Investigator will submit and, if necessary, obtain approval from the above parties for any material changes to the original approved documents, if any.

The principal investigator is obliged to report to the Ethics Committee of Serbia when the study is completed.

15. INFORMED CONSENT PROCESS

1. Description of the general process of obtaining informed consent

Before any study procedure is applied to a subject, the subject's consent to participate in the clinical trial must be obtained. Voluntarily given consent is confirmed by the subject signature in the Informed Consent Form. Interviews with potential respondents regarding the process of obtaining informed consent will be conducted by a qualified and trained doctor, ie the principal investigator or co-investigator (delegated by the principal investigator to conduct interviews and obtain informed consent from potential respondents). The principal investigator or co-investigator, after the process of obtaining consent from the subject, must personally sign and date in the Informed Consent Form.

When conducting an interview with a potential subject, the principal investigator/co-researcher must explain to the subject in his native language, without using professional terms, all aspects of the clinical trial that are relevant for the subject's decision whether to participate in the clinical trial. All the information that will be provided to the respondent during the informed consent discussion is listed in the Informed Consent Form. If the potential subject has any questions regarding the proposed clinical trial, the principal investigator/co-investigator will answer them patiently and understandingly until the subject is satisfied with the answers. The Principal Investigator/Co-Investigator will allow the subject to voluntarily decide whether to participate in the proposed trial and will not in any way coerce, induce, or inappropriately influence the subject to participate in the trial. The principal investigator/co-investigator will provide as much time as is necessary for the subject to read and understand the Informed Consent Form and to consider whether he or she wants to participate in the proposed clinical trial. After a voluntary decision on consent, the subject signs and dates two copies of the Informed Consent Form. Both copies of the document are signed and dated by the Principal Investigator/Co-Investigator. One copy of the signed and dated document is given to the subject by the principal investigator/co- investigator, while the other copy remains at the site of the study. By signing the document, the respondent does not waive any of the rights to which he is entitled by law.

If, during the course of the clinical trial, new information becomes available regarding the tested medical device or the clinical trial that may affect the future health and medical care of the subjects, that is, which may affect the subjects' decision to continue participating, that information will be provided to the subjects in writing.

The following will be discussed with potential study participants:

- Purpose of the research, duration of participation in the study, study procedures, scientific evidence that justifies the conduct of the study and potential risks and potential benefits of participation in the study, side effects that may occur during the study or after it

- It is about Bluetooth data transmission technology from the sensor to the mobile phone and that it has not been shown to have a harmful effect on the morphology and function of the organs, but every situation will be recorded and investigated

- All subjects will receive a test device because it is a study with only one study group

- Participation in the study is voluntary and the potential participant can refuse to participate in the study at any time. Refusing to participate in the study or not agreeing to participate will not affect any other aspects related to his treatment at the clinic

- Participation in the study is free of charge for the respondent

- In certain circumstances, the researcher may withdraw the subject from the study without consent of the respondent

- During the study, the subject will be presented with all findings during the research related to the tested device, and which may influence the respondent's decision to continue the study

- The subject will be informed how many participants will be included in the study

- Subjects will be informed who to contact from the members of the trial team if they want to know more information about the study, the study device, and their rights as a study participant.

- The researcher is responsible for obtaining informed consent prior to the start of participation in the study, which contains the date and signature of the subject participating in the study. The subject will receive a copy of the signed consent to keep, and one signed consent to be kept by the principal investigator as part of the study documentation.

2. Informed consent in special circumstances

In this study, one of the criteria for inclusion is that the respondent is able to voluntarily consent to participate in the study. If for any reason the subject is unable to give voluntary consent, he/she will not be included in the study.

3. Participant confidentiality

By signing the Protocol, the principal investigator agrees that the Protocol, documentation, data and all other generated information will be strictly confidential. The researcher may disclose such information, within regulatory restrictions and ethical considerations, only to regulatory authorities, ethics boards or similar professional boards or commissions, or their institutions (direct or affiliated) and employees. No study-related information or study data may be forwarded to any unauthorized third party without the prior written approval of Sponsor. The principal investigator will ensure that all employees involved in the study respect confidentiality in accordance with all applicable laws and regulations, including the Personal Data Protection Act, Official Gazette of the Republic of Serbia no. 87/2018. Medical information about individual participants obtained during this study is confidential and cannot be disclosed to third parties, except to authorized monitors, auditors or inspectors, or if there is any other situation regulated by law. Confidentiality will be ensured by using study participant numbers to identify each participant; these study participant identification numbers will also be used for participant data in study site participant files and CRFs.

16. ADVERSE EVENTS, ADVERSE EFFECTS OF THE DEVICE AND DEFECTS OF THE DEVICE

1. Adverse event (AE)

An AE or adverse event is:

Any adverse medical event in a patient or other clinical trial participant participating in an investigational medical device that does not necessarily have a causal relationship with the device being investigated.

An AE can therefore be any adverse and unintended sign (including an abnormal laboratory finding), symptom, or illness temporarily associated with the use of a device, whether or not considered device-related.

2. Adverse Device Effect (ADE)

A device side effect is any unwanted response to a medical device.

The term "medical device responses" means that the causal relationship between the test device and the adverse event (AE) is the least possible, ie. that the connection cannot be turned off.

All cases judged by a medically qualified professional or sponsor to have a reasonable suspicion of a cause-and-effect relationship with the device qualify as a device effect.

It also includes any event resulting from defects or inadequacies in the instructions for use or application of the device and includes any event resulting from user error.

3. Device disadvantages

This is a first-in-human study and the device's shortcomings regarding possible risks are detailed in protocol and Brochure for the researcher.

Baby FM DOO has not identified additional defects, and any defect of the device that is recognized during the study will be recorded and explained in the final report of the clinical trial.

4. Serious Adverse Event (SAE)

An SAE is an adverse event that:

- Led to death
- Caused a serious deterioration in the health of the respondent which:
- The result is a life-threatening illness or injury (NOTE: The term "life-threatening" in the definition "serious" refers to an event in which the participant was at risk of

death at the time of the event; it does not refer to an event that could hypothetically have caused death if it had been more severe.)
- The result is permanent damage to body structure or body function
- Required hospitalization or extension of existing hospitalization
- The result of medical or surgical intervention to prevent permanent damage to body structure or body function
- Other important medical events (Other events that cannot lead to death, are not life-threatening or do not require hospitalization, may be considered a serious adverse event when, based on appropriate medical assessment, the event may endanger the patient and may require medical or surgical intervention to prevent one of the above-mentioned outcomes).

In order to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonyms, the following clarification note is provided:

The term "severe" is often used to describe the intensity (severity) of a particular event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical importance (such as a severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria typically associated with events that threaten the participant's life or functioning. Severity (not severity) serves as a guide for defining regulatory reporting obligations.

5. Serious Adverse Device Effect (SADE)

A serious adverse device effect (SADE) is any adverse medical event observed in a patient that can be attributed in whole or in part to the device resulting in the occurrence of a serious adverse event.

A SADE is also any event that could have led to these consequences if no appropriate action or intervention had been taken or if the circumstances had been less favorable.

All cases of SADE are assessed by a medically qualified professional or sponsor.

6. Unintended Adverse Device Effect (UADE)

Any serious adverse health or safety effect of the device or any life-threatening problem or death caused by or related to the device, if that effect, problem or death was not previously determined in nature, severity or incidence in the research plan or application of the device (including a supplemental plan or application), or any other unexpected serious problem associated with the device that affects the rights, safety or welfare of the subject.

7. Reporting of adverse events

All participant- or investigator-reported AEs occurring during the study, whether attributable to the investigational device or not, will be recorded in the CRF as specified in the Clinical Trial Plan. All ADEs will be recorded in the CRF.

The following information related to the event will be recorded:

- description
- start date and end date
- seriousness
- assessment of association with the device, other suspected drug or device
- measures taken
- More detailed information will be attached as needed.

The relationship of the AE to the device will be evaluated by a medically qualified investigator or the sponsor / manufacturer and will be monitored until resolution of the adverse event is considered stable.

All ADEs that result in participant withdrawal from the study or are present at the end of the study should be followed up until satisfactory resolution occurs.

The person responsible for reporting adverse events in this clinical trial is Prof. Dr. Ivan Soldatović.

8. SAE / SADE / UADE application procedures

1. SAE reporting authority

Baby FM was authorized by Prof. Dr. Ivan Soldatović to coordinate the reporting of adverse events.

2. Reporting of serious adverse events (SAEs) by investigators

The investigator is required to immediately report any adverse event considered serious, either whether it is connected to the tested device or not.

The researcher is obliged to fill out the SAE form and send it to Prof. Dr. Ivan Soldatović by e-mail.

The researcher should not delay the application of the SAE due to the possible waiting for additional information. It is more important that the investigator reports the event, even if some information is missing, and then can subsequently report additional information related to the adverse event that is collected during patient follow-up.

3. Reporting an adverse event to a regulatory body

Baby FM doo authorized prof. Dr. Ivan Soldatović as the person responsible for reporting SAE to ALIMS and the Ethics Committee of Serbia. Prof. Ivan Soldatović, Ph.D., will immediately report a serious adverse event to ALIMS and the Ethics Committee of Serbia.

4. Reporting of adverse events

All adverse events (SAE and AE) will be reported to the Ethics Committee of Serbia, in accordance with the time frames prescribed by the committee. The researcher is responsible for reporting all events to the sponsor and the responsible body within the stipulated time frame.

9. Device defect reporting process

Reporting of possible device defects will be in the form of tables containing the following information:

- Serial number of device shortage
- Description of the device defect
- Impact of the flaw on device security
- The effect of the deficiency on the efficiency of the device
- A possible solution to eliminate the deficiency

The principal researcher is obliged to report any defects of the device to the sponsor within 7 days, all with the aim of possible elimination of the defect during the study, or after the end of the study.

10. List of expected adverse events and expected side effects of the device

Although the device is considered safe (by the sponsor), there are expected adverse events, i.e. expected side effects of the device.

They are:

- After wearing the system for several hours, there is a possibility that they will remain for several minutes after removal, marks on the skin where the tape and sensor were. The traces will disappear by themselves after uninstalling the system.
- In the event that the material of the band (sensor carrier) creases while lying down, there is a possibility of a slight redness in the place where the irritation (scaling) occurred. The redness should disappear soon after the pressure is released.
- If a person were to sleep on the wrong side (side), there is a possibility that redness of the skin will appear in the armpit as a result of the pressure of the sensor on that place. It is expected that this redness is short-lived and will subside as the skin is relieved of the pressure in the area.

- If the person is not aware of the existence of an allergy to elastin, metal or silicone and the anamnestic information yes there is no allergy, there may be skin irritation in the place where the tape and sensor are placed. This effect is expected to disappear within a few hours without the need for therapy.

11. Security Data Oversight Board

A safety data monitoring committee will not be organized at this stage of the study because it is estimated that there is minimal risk associated with the use of the investigational medicinal product, the expected adverse events are skin reactions at the point of contact of the medicinal product with the subject's skin, and people with chronic diseases, who will be included in this trial, will not be people with a high-risk medical condition (see section 17). Data security will be evaluated upon completion of the study.

12. Interim analysis

No interim analysis is planned at this stage of the adult body temperature measurement system trial.

17. VULNERABLE GROUPS

In this study, it is planned that the majority of subjects will be subjects who are not members of vulnerable groups.

The only possible members of vulnerable groups, who will be included in the above-mentioned clinical examination, are persons with chronic diseases and with a mild or moderately severe general condition (a patient who is communicative, cooperative). In the internal department of the clinic, mostly patients who have a chronic disease lie, and most often they are hospitalized due to its exacerbation. For this reason, patients with chronic diseases will be included in the study, but the study procedures do not affect in any way the course of diagnosis and treatment of these patients at the clinic.

The principal researcher and other members of the research team are obliged to treat the representatives of the vulnerable group with care, respect, fairness, allowing free will, excluding any form of encouragement to participate in the research.

The principal investigator and ethics committee are responsible for protecting the rights, safety, dignity and well-being of all clinical trial subjects. The principal researcher will pay special attention to the protection of the interests of the respondents when including people with chronic diseases. People with a high-risk medical condition, people who are in intensive care, people who are in such a condition that may interfere with their autonomy, understanding the essence of the trial or decision-making ability, people who are not able to independently give their consent to participate and independently sign the Informed Consent Form, the principal investigator or co-investigator (delegated by the principal investigator to conduct informed consent discussions with potential subjects) will not be included in this clinical trial. When conducting interviews with all potential subjects, and especially with people with a chronic disease, the principal investigator or co-investigator will unequivocally tell potential subjects all information related to the course of the clinical trial, that they will not have direct benefits from this trial, all possible risks, that they will not be paid for participation in this clinical trial and that if they do not agree to participate in this clinical trial and if they agree, but at any time change their mind and withdraw their voluntarily given consent, there will be no impact on their health care.

The expected level of risk to subjects in this clinical trial is low. Clinical trial participants will be observed by qualified clinicians during and after using the investigational medicinal product. The chief researcher will pay special attention to people suffering from chronic diseases. The main researcher will monitor and talk to the subjects every day during the study and if he assesses the feeling of dissatisfaction, discomfort or an increased level of risk in any subject, he will exclude him from the study with the explanation that he is acting in order to protect his well-being.

If there is a febrile convulsion or any other complication of the underlying disease, a sudden worsening of the health condition due to the underlying disease, or any systemic reaction during temperature measurement, the tested medical device is removed from the subject, he/she stops further participation, and will be patient until the condition stabilizes. Given that the respondents are already hospitalized, possible emergency assistance will be

immediately available to the respondents if needed. If additional emergency care or resources are needed, depending on the case, the respondent will be provided with emergency care and transport to a hospital of another level (ie another specialty) if necessary and at no cost to the respondent.

It is the principal investigator's responsibility to continuously monitor, assess and document the level of risk. In the event of a higher level of risk than estimated or the occurrence of an unusually high rate of serious adverse events (SAE) or in the event of an SAE leading to death or any safety reason, the principal investigator is obliged to suspend or temporarily terminate the clinical trial and to inform the Sponsor, the regulatory body and the Ethics Committee of Serbia. In that case, the clinical trial will be suspended until the Sponsor, the regulatory body and the Ethics Committee of Serbia review the relevant data and agree that the clinical trial can continue.

The trial team will be qualified by experience, education and training to carry out all activities for which they are responsible in the conduct of the clinical trial. All clinical trial participants (those responsible for designing and conducting the clinical trial) will undergo GCP (Good Clinical Practice) training before the clinical trial begins. Additionally, the trial team will receive training related to all procedures consistent with their role in the clinical trial.

By signing the Clinical Trial Plan, the Principal Investigator agrees that the Clinical Trial Plan, documentation, data and all other information generated will be strictly confidential. The principal investigator will ensure that the investigation team respects confidentiality in accordance with all applicable laws and regulations, including the Personal Data Protection Act, Official Gazette of the Republic of Serbia no. 87/2018. Participant information obtained during this clinical trial is confidential and cannot be disclosed to third parties, except for authorized monitors, auditors or inspectors, or if there is any other situation regulated by law. Confidentiality will be ensured by using clinical trial participant numbers to identify each participant. Also, when publishing the results of the clinical trial, no subject will be identified.

After the completion of the clinical examination for each subject, the measurement of body temperature (if necessary) continues with a standard thermometer. After the use of the investigated medicinal product, a three-day monitoring period of the subject is foreseen. If the subject has any unwanted events during or after the planned monitoring period, he will be provided with adequate health care and, if necessary, treatment until the condition is resolved or stabilized.

18. SUSPENSION AND/OR EARLY TERMINATION OF THE CLINICAL TRIAL

Sponsor Baby FM DOO, the regulatory body, or the Ethics Committee of Serbia, or the principal investigator may suspend the clinical trial at any time for any safety reason. This includes, for example, and without limitation, an SAE leading to death or an unusually high rate of SAE.

In case of new data indicating an increased level of risk for the involved participants, the clinical trial will be suspended until Baby FM DOO, the regulatory body of Serbia and the Ethics Committee of Serbia review the relevant data and agree that the clinical trial can continue.

If the clinical trial is suspended or prematurely terminated by Baby FM DOO, Baby FM DOO will inform the principal investigator, the regulatory body and the Ethics Committee of Serbia about the decision and the reasons for the termination or suspension. If such action is taken, every effort must be made to ensure the safety of participants involved in the clinical trial. The Regulatory Body and the Ethics Committee of Serbia will be notified of the decision and reasons for the termination or suspension of the clinical trial within 15 days from the day of suspension of the trial.

19. ACCESS TO CLINICAL DOCUMENTS

The principal investigator agrees to allow the monitor, auditor, trial institution authorities and regulatory authorities direct access to all relevant documents in order to conduct monitoring, audits and inspections related to the clinical trial.

20. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

1. General considerations

The study will be conducted in accordance with the current approved Clinical Trial Plan, Good Clinical practice and all regulations of the Republic of Serbia.

The study team will follow the study procedures detailed in the Clinical Trial Plan. All team members must undergo mandatory study implementation training according to the Clinical Trial Plan, before subject recruitment can begin.

Study data from the CRF will be entered into the electronic database. The database listing will be revised and corrected during data collection and until the database is closed. Once all disputed data collected in the study are resolved, the database will be locked and no further changes to the data will be made.

Quality control will be carried out in accordance with the law and regulations.

The study team will adhere strictly to the procedures outlined in the Clinical Trial Plan. All team members must complete mandatory study-specific training prior to the initiation of subject recruitment, as stipulated in the trial protocol.

2. Training

All members of the study team will be trained to fulfill the responsibilities provided for in the Clinical Trial Plan, and in accordance with their responsibilities in the study. The study monitor is in charge of revising and possibly repeating the staff training, if he judges that there is a need for it.

21. HUMAN RESOURCES INCLUDED IN THE STUDY

The study team will be qualified to participate based on experience, education and training to carry out all activities for which they are responsible in conducting the study

All participants in the study (those responsible for the design and implementation of the study) will undergo GCP (Good Clinical Practice) training before the study begins. Additionally, study staff will receive training related to all procedures consistent with their role in the study.

22. CLINICAL STUDY REPORT AND PUBLICATION OF RESULTS

The Clinical Study Report (CSR) presenting the research results consists of text and tables reflecting all safety and security related results and will be generated by AXSIOM International doo

All data, documents, all recordings and information transmitted to any contractor or obtained or prepared by any contractor, its consultants or third parties contracted to participate in the study, during the trial, belong to the Sponsor.

After the completion of the clinical study report, the researchers, together with the sponsor, are expected to publish the results (negative or positive) of this study in a peer-reviewed scientific journal. Sponsor may not prohibit public publication of the results of this trial.

Publication of study results will be the responsibility of the Principal Investigator. Other authors will make up the team that is participated in organizing the study, arranging and processing the data, as well as writing the publication.

In the Acknowledgments section, Baby FM Doo will be listed as a company that helped conduct the study and publishing results.

All costs of publication in the medical journal will be borne by Baby FM Doo.

23. LITERATURE

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