TESTING THE TELEMEDICE SYSTEM FOR CONTINOUS FEVER MONITORING IN ADULTS – THE PILOT STUDY

Statistical Analysis Plan v1.0

Belgrade, 2025

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1. Administrative Study Information

1.1. Document Description

The purpose of this document is do describe all statistical methods and procedures that will be applied for data analysis in BABYFM-010 clinical trial "**TELEMEDICINE SYSTEM TEST FOR THE CONTINUOUS BODY TEMPERATURE MONITORING IN ADULTS - A PILOT STUDY"**.

This Statistical Analysis Plan (SAP) for the BABYFM-010 study is prepared in compliance with ICH E9, ISO 14155:2020, and JAMA guidelines. The document is based on the protocol version 3.0.

1.2. Clinical Trial Registration

Trial Acronym	BABYFM-010
Protocol Version	3.0
Protocol Date	29-FEB-2024
NCT number	NCT06447337
Clinical Phase	Pivotal
Lead Sponsor	Baby FM DOO

1.3. SAP Informations

Version	1.0
Date	18-Oct-2025

1.4. Document Approval

The Statistical Analysis Plan for BABYFM-010 clinical trial has been approved by:

Date:

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Savo Papić
Baby FM DOO
Chief Executive Officer

Date:

_____

Doc Dr Nikola Mitrović
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2. Introduction

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.

2.1. Study Background and Rationale

All the guides suggest measuring the temperature in the axillary position (under the armpit) during the illness with elevated body temperature. Today, the digital thermometer is the gold standard.

Continuous monitoring of babies' body temperature in real time would avoid a lot of problems and mistakes caused by parents. 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 outside of hospitals, 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.

Sleepless nights, stress and uncontrollable 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.

One of the problems with existing devices (which use patches to position sensors) is irritation of the baby's skin with the adhesive, which can result in contact dermatitis and allergies. The problem with non-stick devices is poorer contact and efficiency with satisfactory safety.

The biggest problem to be solved is accurate, continuous monitoring of temperature in real time, which will result in maximum safety of babies and peaceful sleep of parents.

2.2. The Investigational Product

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.

2.3. Risks and Benefits

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
- Easier communication with clinical trial subjects

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.

Also, respondents who participate in this phase of the clinical trial can help children and parents in the future because accurate, continuous temperature monitoring in the real time would result in maximum safety for babies and peaceful sleep for parents.

The only expected side effect in this trial is skin irritation on the place of the device position. It is expected that a fabric that contains a high percentage of cotton and a low percentage of elastin should not cause any reaction on the skin. The device is covered with medical silicone, which further reduces the chance of causing any irritation. Finally, the contact sensor located in the armpit is made of metal and, also, should not cause any irritation.

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.

2.4. Objectives and Outcomes

The clinical trial BABYFM-010 has defined primary and secondary objectives.

2.4.1. Primary Objectives and Outcomes

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 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

- safety

The safety is examined by assessing the frequency of adverse events during maximum 72 hours while wearing the device and during 72 hours from the moment of removing the tested device.

- System performance

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

2.4.2. Secondary Objectives and Outcomes

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

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
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3. Study Methods

3.1. Trial 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.

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.

3.2. Randomization and Blinding

This is non-randomized non-blinded clinical trial.

3.3. Sample size

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.

4. Study Subjects

4.1. Definition of Compliance and Protocol Deviations

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.

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.

4.2. Analysis Populations

4.2.1. The Study Populations

The study has two subjects populations:

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

Safety 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).

4.3. Eligibility and Withdrawal Criteria

4.3.1. Eligibility 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)

The criteria for exclusion in the study are:

- 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

4.3.2. Subjects Withdrawal

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.

5. Statistical Methods

5.1. Primary Objective

The primary efficacy objective in this clinical trial is to assess the accuracy of the body temperature measurements of Baby FM investigational medical product and to compare it to the registered comparator. The correlation between devices has been chosen as a measure of agreement between devices.

The primary safety objective in this clinical trial is to assess frequency of the adverse events. The frequency will be assessed using adverse events form.

The primary performance objective is to assess whether the investigational medicinal product properly functioning by evaluating any deviation from the intended functioning, defined in protocol.

5.2. Hypothesis

The efficacy 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).

5.3. Analytical Procedure to Evaluate Primary Objectives

5.3.1. Primary Efficacy Objective

The primary efficacy objective is the agreement in temperature value between investigational medical product and comparator. The comparator is gallium thermometer. The evaluation of agreement will be tested using following statistical procedures:

- Linear correlation
- Linear regression
- Scatter Plot
- Distribution of value difference
- Histogram of the distribution of value difference
- Bland-Altman Plot

It is expected that values have linear correlation and that slope in regression analysis will be close to 1. The expected mean difference between values should be nearly 0. It is expected that Bland-Altman plot reveals no systematic difference (points to be randomly scattered).

5.3.2. Primary Safety Objective

The primary safety objective will be assessed using frequency and percent of adverse events. The analysis of AEs will be based on the concept of treatment-emergent AEs (TEAEs), adverse device effects (ADE), and serious adverse device effects (SADE). All analyses of AEs will be based on the number of patients with AEs per medical device used.

AEs will also be analysed with respect to their duration, outcomes, seriousness, severity, frequencies, action taken, relationship to study treatment, as well as the date and time of resolution. If an AE is serious, an analysis of the criteria for seriousness will be performed.

5.3.3. Primary Performance Objective

The primary performance objective will be assessed using frequency of the non-anticipated performance of the device. Device deficiencies will be analyzed with respect to any inadequacy in measurement, quality, durability, safety or performance which includes malfunction, errors and other inadequacies.

5.4. Analytical Procedures to Assess Secondary Objectives

Secondary outcomes include anxiety of the participant and patient comfort during measurement. Both will be measured by a short questionnaire with questions about user experience while using the continuous temperature measurement system.

The frequency of each response will be presented using count and percent.

5.5. Confidence Intervals

All results regarding the primary efficacy and safety endpoints will be presented as point estimate (proportion, mean, median) with two-sided 95% confidence interval.

5.6. Sensitivity Analysis Plan

No sensitivity analysis is planned for BABYFM-010 clinical trial.

5.7. Interim Statistical Analysis

No interim analysis is planned for BABYFM-010 clinical trial.

5.8. Subgroup Analysis

No subgroup analysis is planned for BABYFM-010 clinical trial.

5.9. Missing Data

No imputation of missing data will be performed in BABYFM-010 clinical trial.

5.10. Adjustment for Multiplicity and Type I Error Control

Adjustment for multiplicity and type 1 error control are not planned for the BABYFM-010 clinical trial.

5.11. Statistical Software

All data will be analyzed using R 4.5.0 statistical software (R Core Team (2025). _R: A Language and Environment for Statistical Computing_. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org)

6. Presentation of the Results

6.1. Baseline characteristics

The following patient characteristics will be presented during screening:

- Age
- Gender
- Body Measurements (height, weight, BMI)
- Medical History
- Concomitant Medications

Nominal endpoint variables will be presented using frequency count and percent. Ordinal variables with sufficient number of categories will be treated as numerical, while ordinal variables with small number of categories will be treated as nominal. Numerical (continuous) endpoint variables will be presented as mean, standard deviation, standard error of mean, 95% confidence interval for mean, minimum, median, 25th percentile, 75th percentile, and maximum.

Medical history and concomitant medications will be presented as count and percents as well as data listing.

6.2. Primary Endpoints Evaluation

6.2.1. Efficacy Evaluation

The efficacy evaluation will be performed using

- Descriptive statistics
- Pearson correlation analysis
- Linear regression analysis
- Scatter Plot
- Mean difference between methods
- Bland-Altman Plot

Numerical (continuous) endpoint variables will be presented as mean, standard deviation, standard error of mean, minimum, median, 25th percentile, 75th percentile, and maximum. Pearson correlation analysis will be presented using r coefficient, while linear regression will be presented using alpha and beta coefficients. Both will be supported with hypothesis testing.

Mean difference between methods will be presented as descriptive statistics and paired samples t test.

Bland-Altman plot will be constructed as mean difference on x axis and average of the methods on y axis. The dashed lines will be used to present mean and 95% CI for the average.

Scatter plots will be presented for all subjects and for each subject. All subjects scatter plot will contain reference medical product on x axis and investigational medical product (Baby FM) on y axis. Regression line will be used to show average relationship between devices. Scatter plots will be presented for all measurements and for adequate measurements (measurements where the device is on position, no deviations during measurements etc.). For each subject, the measurements will be presented as time on x axis and measurements of both devices presented in different color.

6.2.2. Safety evaluation

The safety evaluation will include:

- Occurrence of adverse events
- Occurrence of serious adverse events
- Frequency, relatedness and action taken of adverse events
- Listing of adverse events
- Criteria of seriousness for serious adverse events

Results will be presented as counts and percents.

6.2.3. Performance evaluation

The performance evaluation will include:

- Device deficiency (structure deficiencies)
- Connection error
- Measurement error (impossible values)

Results will be presented as counts and percents.

6.3. Secondary Endpoint Evaluation

Secondary endpoints are anxiety due to wearable device placed on the body and continues measurements, and patient comfort while using continuous temperature measurement system.

Questionnaire will be applied to participant and answers will be recorded using ordinal scale.

Both will be presented tabular, using count and percents.

7. Data Management and Quality Assurance

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.

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.

8. Tables, Listings and Figures

The numbering of the planned tables, figures and listings in this clinical trial are presented in accordance with ICH E3 Guideline Structure and the Content of Clinical Study Reports.

8.1. Tables

8.1.1. Baseline characteristics

1	Age (descriptives)
2	Gender (n, %)
3	Anthropometry (height, weight, BMI)
4	Constitution
5	Known allergies (n, %)
6	Anatomical anomaly (n, %)
7	Health risk (n, %)
8	Pacemaker (n, %)
9	Comorbidities (Y/N) (n, %)
10	Comorbidities (listings)
11	Hair on the axillary position (n, %)
12	Allergy on cotton, metal or silicon (n, %)
13	If yes, what allergies (listing)
14	Known skin reactions (n, %)
15	If yes, what known skin reactions (listing)

8.1.2. Clinical characteristics

1	Diagnostics for the primary disease completed
2	Primary diagnosis (listing)
3	Current therapy (listing)
4	Fever therapy (n, %)
5	Visible signs on skin where sensor will be placed (n, %)
6	Enrollment criteria met (n, %)

8.1.3. Sensor placement and removal

1	Skin changes on sensor position (n, %)
2	Skin changes on sensor position (listing)
3	Symptoms during measuring temperature (n, %)
4	Symptoms during measuring temperature (listing)
5	Patient concluded the study as planned (n, %)

6	If not, reasons why the participant did not conclude the study as planned (listing)

8.1.4. Primary Endpoint – Temperature Measurements

1	Baby FM and Gallium Thermometer Values (descriptives)
2	Baby FM and Gallium Thermometer Values (boxplot)
3	Difference between Test and Reference IMP (histogram)
4	Paired samples t test for difference between Test and Reference IMP
5	Baby FM Thermometer Values by Adequate Postiton (descriptives)
6	Test vs. Reference difference (n, %)
7	Test vs. Reference difference +/- 0.5 (n, %)
8	Test vs. Reference difference +/- 1 (n, %)
9	Test vs. Reference IMP (scatter plot)
10	Test vs. Reference IMP (only adequate measurements) (scatter plot)
11	Test vs. Reference IMP correlation analysis
12	Test vs. Reference IMP correlation analysis (only adequate measurements)
13	Test vs. Reference IMP regression analysis
14	Test vs. Reference IMP by Subject (scatter plots)
15	Test vs. Reference IMP by Subject (correlation)
16	Bland-Altman Plot for Test vs Reference IMP
17	Bland-Altman Plot for Test vs Reference IMP (only adequate measurements)

8.1.5. Primary Endpoint – Safety analysis

1	Occurrence of AEs (n, %)
2	AE (listings)
3	Frequency of AEs (n, %)
4	Relatedness to IMP (n, %)
5	Serious AE (n, %)
6	Action Taken (n, %)

8.1.6. Primary Endpoint – Performance

1	Structural damage (n, %)
2	Structural damage (listing)
3	Connection problems (n, %)
4	Connection problems (listing)
5	Invalid values (n, %)
6	Invalid values (listing)

8.1.7. Secondary Endpoints - Questionnaire

1	Strip too tight (n, %)
2	Material not comfortable (n, %)
3	Itching (n, %)
4	Sweating (n, %)
5	Blistering (n, %)
6	Blistering on the sensor position (n, %)
7	Pain (n, %)
8	Anxiety (n, %)
9	Scared (n, %)
10	Discomfort (n, %)
11	Comments (listing)

8.2. Listing

8.2.1. Baseline Characteristics and Enrollment

1	Age, Gender and Anthropometry
2	Diagnostics performed and availability for frequent measurements
3	Known allergies, Anatomical anomalies, High health risk and Pacemaker
4	Constitution
5	Hair level
6	Allergy on used materials and other allergies
7	Previous skin reactions
8	Current therapy
9	Fever therapy
10	Visible signs on skin where sensor will be placed
11	Enrollment criteria met

8.2.2. Clinical characteristics during measurements

1	Skin changes on place where sensor was placed
2	Symptoms during the study
3	Study finished as planned

8.2.3. Questionnaire

1	Questionnaire answers
2	Comments

8.2.4. Temperature measurements

1	Test and Reference IMP measurements used in the analysis with adequate position of the sensor
2	Comments