Document Description: TIMMY3 80601-2-56:2017 + A1 2018	Document Number: 60128116 Version: C
Hill-Rom	Page 1 of 32
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Author: [redacted]

Version	Sec, Pg, Para Changed	Description of Change	Reason for Change	Date Version Created	Version Created By (initials)
A	All	Initial Release	Initial Release	[redacted]	
B	Section VIII – A (Page 15) Section VIII – B (Page 16) Section X – H (Page 27) Section X – J (Page 28) Appendix A (Page 29) Appendix B (Page 32)	Removed sentence "The subject will be noted…" Changed description of assigning Subject ID number Added Device Deficiency Review section Added Protocol Violations/Deviations section Revised Subject ID # format & added Informed Consent Date Added "Stop Time" fields to Data Form Remove: Data Collection Tool SW Version:	All changes are derived from Safety Management Plan and/or Case Report Form specifications No Data Collection Tool for this study	[redacted]	
C	1,2,3 -Section V – C Subject Selection Criteria	Subject Inclusion Criteria 1. 1st bullet – replaced 'between 7 and 17 years of age must provide assent to participate in the study." with "minors must provide assent according .."	1, 2, 3 - Align with clinical site IRB approved ICF & to clarify language	[redacted]	

	4 & 5 - Appendix A: Sample Study Subject Eligibility Form	2. 2nd Bullet – replaced "Subjects must be able to provide an informed consent or have legally authorized representative consent to participate" with "Subject or the legally authorized representative (LAR) must sign.." Subject Exclusion Criteria 3. Removed "The study subject or their legally authorized representative (LAR) refuses to allow the study subject to participate for any reason." 4. #5 Replaced "able to give consent" with "signs the ICF" 5. #7 Removed "between 7 and 17 years of age must provide assent to participate in the study." and added "minors must provide assent according to the clinical site's policy.."	4 & 5 - To match Subject IC in Section V - C		

Required Approvers		
Function:	**Name:**	**Signature/Date:**
[redacted]		

D* See SAP system for Change Number, Approver(s) Name, and Date(s) of Approval.

[redacted] Products:	[redacted]
Protocol Number:	60128116 v. C
Sponsor's Investigator:	[redacted]
Sponsor's Clinical Project Manager:	[redacted]
Sponsor:	[redacted]

Contents

I. General Information

A. Purpose

The purpose of this document is to validate the clinical accuracy of the TIMMY3 thermometry module, integrated into host device CVSM, according to 80601-2-56:2017 + A1 2018.

This study is designed to provide supporting documentation for the TIMMY3 module operating with SureTemp Plus algorithms. Testing will be performed with a production equivalent CVSM modified to use TIMMY3 (TIMMY3 investigational device), running the SureTemp Plus algorithms. The TIMMY3 module is intended to be integrated into additional [redacted] devices such as, but not limited to, the Connex Spot Monitor and Spot 4400. The process described below will be followed in accordance with the method called out in ISO 80601-2-56:2017 + A1 2018.

B. Intended Use, Indications for Use, Intended Purpose

TIMMY3 Investigational Device (Connex Vital Signs Monitor modified to include TIMMY3)

- **Intended Use**: TIMMY3 is an electronic thermometry module integrated into a host device and provides predictive and direct measurements at Oral, Axillary, and Rectal subject sites.
- **Indications for Use**: TIMMY3 provides interfaces to allow the host device to implement predictive and direct measurements of the Oral, Axillary, and Rectal subject sites.

  TIMMY3 is intended to be used by clinicians and medically qualified personnel for monitoring of body temperature in neonatal, pediatric, and adult subjects. TIMMY3 supports subjects from birth to end of life depending on algorithm and subject site.

Connex Vital Signs Monitor 6000

The Connex Vital Signs Monitor 6000 series of monitors is intended to be used by clinicians and medically qualified personnel for monitoring of neonatal, pediatric, and adult subjects for:

- Noninvasive blood pressure (NIBP)
- Pulse Rate (PR)
- Noninvasive functional oxygen saturation of arteriolar hemoglobin (SpO2)
- Body temperature in normal and axillary modes

- **Intended Use Environment**: The most likely locations for subjects to be monitored are general medical and surgical floors, general hospital, and alternate care environments.
- From the temperature frame you can measure the subject's temperature. The temperature frame contains data and features relevant to temperature measurement. The frame provides different features based on the profile you are using. (Oral, axillary, rectal)

- **Contraindications**: Inaccurate measurement risk. To ensure optimal accuracy, always confirm that the correct mode and site are selected.

  The thermometers used in this study are Class II medical devices.

C. Determination of Nonsignificant Risk Investigation

The risks associated with the TIMMY 3 investigational device were assessed and documented in the TIMMY 3 Hazard Analysis, [redacted] All hazards and risks are accounted for in this protocol. The Hazard Analysis supports the determination that this study is not a significant risk (NSR) study per 21 CFR 812.3(m).

For detailed risk analysis and risks for the investigational device see CVSM Risk Assessment Summary (RAS), [redacted] Potential hazards for the TIMMY 3 investigational device were identified in the TIMMY 3 Hazard Analysis [redacted] with risk acceptance occurring in the CVSM RAS.

This study is a Non-Significant Risk (NSR) Investigation because the study devices do not present a potential for serious risk to the health, safety, or welfare of the subject. The study devices are not implants, do not support, or sustain human life, and are not substantially important in diagnosing, curing, mitigating, or treating disease or in preventing impairment to human health.

This testing does not represent a potential for serious risk to the health, safety, or welfare of a subject. This assessment is based on the Code of Federal Regulations, Section 21, Part 812, Subpart A, as the testing:

- Is non-significant risk. The components involved such as the probe and probe covers are released products, it is the algorithm that is being validated.
- Does not require an invasive sampling procedure that presents significant risk.
- The devices are not used in sustaining or supporting human life.
- Does not by design or intention introduce energy into a subject.
- During this testing, no reliance will be made on data collected via the thermometers for the purpose of making a medical diagnosis.
- Risks are minimized by using procedures which are consistent with sound research design and already being performed on the subject in the clinical environment.

Furthermore, testing will be performed with intended users in their respective intended use environments and the data collected will not be used for clinical diagnostics or subject management.

D. Compliance Statement

This study will be conducted in compliance with this study protocol and the following Hill-Rom Standard Operating Procedures:

- [redacted]

Institutional Review Board (IRB) approval must be obtained from each institution's IRB of record. Institutions that do not have an IRB of record may use an independent IRB that meets all requirements of the U.S. Department of Health and Human Services (HHS) regulations on human subject protection (45 CFR §46) (i.e., studies conducted at Hill-Rom facilities, private clinic, or doctor's office).

Health Insurance Portability and Accountability Act (HIPAA) authorization will be required as health information will be obtained from human subjects.

E. Publication and Disclosure

[redacted]

Information from this study may be posted on publicly available clinical trial registers in accordance with applicable laws and regulations. The data generated by this study is the property of the Sponsor. This data may be used by the Sponsor, now and in the future, for presentation or publication at the Sponsor's discretion or for submission to regulatory agencies. In addition, the Sponsor reserves the right of prior review and approval of data from this study relative to the potential release of proprietary information to any publication or for any presentation.

II. Study Objectives

A. Primary Objective/Endpoint

The primary objective of this protocol is to validate the clinical accuracy of the TIMMY 3 thermometer algorithm on all age groups in the oral, adult axillary, pediatric axillary, and rectal temperature modes. Clinical accuracy will include measurement of clinical bias, with its limits of agreement, and clinical repeatability as defined by the ISO 80601-2-56:2017 + A1 2018.

III. Study Design

A. Equipment

The equipment that may be necessary for conducting the procedures outlined in this protocol is outlined below.

Note: additional equipment that is not listed here may be necessary to complete testing. The equipment used during testing will be documented on the corresponding Device Accountability Log.

- CVSM TIMMY 3 thermometry algorithm
- Probes and probe wells for oral/axillary (blue)
- Probes and probe wells for rectal (red)
- Probe covers
- Cleaning and disinfectant wipes
- Calibrated Stopwatch (as applicable)

- Power strip (as applicable)
- Lubricant jelly for rectal temperatures
- Misc. equipment will be noted on the device tracking form.

The sponsor, [redacted] will supply the equipment to conduct the study. Two Connex Vital Sign Monitors (CVSM) will be provided to each site. One CVSM is considered a back-up device in case a device malfunctions. All CVSM devices and accessories will be returned to the Sponsor at the end of the study.

B. Design

Study Design

The purpose of this document is to test the CVSM with the new integrated TIMMY 3 thermometry algorithm technology for clinical accuracy according to ISO 80601-2-56:2017 + A1 2018. Clinical accuracy will include measurement of clinical bias, with its limits of agreement, and clinical repeatability.

This study is designed as a multi-clinician, multi-center study, multi-person, non-randomized study in alignment with the ISO 80601-2-56:2017 + A1 2018.

Febrile is defined as follows:

- Oral febrile is defined as a 3-minute monitor (Direct) mode temperature of 37.5°C (99.5°F) or greater.
- Adult/Pediatric Axillary Febrile is defined as a 5-minute monitor (Direct) mode temperature of 37.2°C (99.0°F) or greater.
- Rectal febrile is defined as a 3-minute monitor (Direct) mode temperature of 38.0°C (100.4°F) or greater.

The study design includes the following:

- All temperatures will be measured in °C.
- Subjects will be screened for study eligibility by determining that no contraindications to temperature measurement (as appropriate per oral, rectal, or axillary site) exist.
- Study subjects may only be enrolled once per anatomical site. A single subject may be enrolled in the oral, and/or axillary, and/or rectal site.
- For oral, rectal, or axillary sites, each enrolled subject will undergo a predictive (adjusted) mode temperature measurement followed immediately by a Monitor (Direct) mode temperature measurement with the same instrument, without moving the probe position. Monitor (Direct) mode temperature must be 3 minutes for oral and rectal temperatures and 5 minutes for axillary temperatures. The Monitor (Direct) mode temperature will be timed by a calibrated stopwatch.

The following 2 predictive (adjusted) temperatures will be acquired in the same site with a minimum of 1 minute in between readings using a calibrated stopwatch.

• The clinicians will wait a minimum of 3 minutes before taking the next temperature on a different subject with the same probe. This will minimize the possibility of collecting data from a site or a probe still physiologically impacted by the previous temperature measurements.

[redacted] Subsequent reports will in no way identify a subject.

• The total duration of subject participation in this study may last approximately 20-30 minutes for the collection of a data set per anatomical site.

• Study clinicians will be trained extensively on the proper operation of the thermometers.

• This protocol, informed consent and any subject facing materials will be reviewed by an Internal Review Board in the US (IRB)

• Devices used in this study will not be marketed or sold, nor used on subjects except under the procedures set forth in this protocol.

• All devices will be labeled as “Investigational Device."

• All devices will be accounted for upon delivery and through the entire study by the study investigator. The investigator will maintain a log identifying each clinical device by software version and serial number and its location until the devices are returned to the study sponsor.

The CVSM thermometer operates in a Predictive (Adjusted) Mode and a Monitor (Direct) Mode. Predictive (Adjusted) mode temperatures are determined by measuring the rate of change of the sensor’s output and using that information to anticipate or predict the final equilibrium temperature for the site it is measuring.

• **Oral Reference Temperature** is defined as 3-minute monitor (Direct) mode temperature taken in the left or right posterior, medial, sublingual pocket. The oral reference temperature will be done on subjects 5 years of age and older.

• **Rectal Reference Temperature** is defined as 3-minute monitor (Direct) mode temperature taken in the rectum. The rectal reference temperature will be done on subjects of all ages.

• **Adult Axillary Reference Temperature** is defined as 5-minute monitor (Direct) mode temperature taken in left or right axilla. The adult axillary reference temperature will be done on subjects 18 years of age and older.

• **Pediatric Axillary Reference Temperature** is defined as 5-minute monitor (Direct) mode temperature taken in left or right axilla. The pediatric axillary reference temperature will be done on subjects 17 years of age and younger.

• **Note 1**: Whenever possible temperatures will be obtained from subjects of all ages. Oral temperatures, however, may be inappropriate for children under 5 years of age since they may not be capable of keeping the probe in the mouth for three minutes.

• **Note 2**: Monitor (Direct) mode reading times will be timed using a calibrated stopwatch.

• **Note 3**: It is [redacted] position, based on 15 years of historical testing, that oral and rectal thermal equilibrium are attained in 3 minutes and axillary thermal equilibrium is obtained in 5 minutes.

1. Sample Size Justification

Sample size is determined per ISO 80601-2-56:2017 + A1 2018 - Human Subject population requirements.

80601-2-56:2017 + A1 2018

Age group	Age[11]
A1	0 up to 3 months
A2	3 months up to 1 year
B	older than 1 year and younger than 5 years
C	older than 5 years

For example, when consulting the table above:

If subject is 3 months of age, he/she will fall in Age group A2 and if a subject is 1 year old, he/she will fall into Age group B.

The total number of subjects per measurement mode (oral, pediatric axillary, adult axillary, or rectal) is required to be at least 105. The total expected enrollment is 420 subjects for all four (4) modes.

At least 35 subjects are required for each age group A, B, and C if the measurement mode supports that age group. For group A there is an added requirement that subgroups A1 and A2 each need to have at least 15 subjects.

For any group or subgroup, a minimum of 30% and a maximum of 50% of the subjects need to be febrile.

Febrile is defined as follows:

- Oral febrile is defined as a 3-minute monitor (Direct) mode temperature of 37.5°C (99.5°F) or greater.
- Adult/Pediatric Axillary Febrile is defined as a 5-minute monitor (Direct) mode temperature of 37.2°C (99.0°F) or greater.

- Rectal febrile is defined as a 3-minute monitor (Direct) mode temperature of 38.0°C (100.4°F) or greater.

Oral supports age group C as 5 years old and greater

Pediatric axillary supports A1, A2, B, and C where C contains subjects between 5 years and less than 18 years old.

Adult Axillary supports group C where C contains subjects 18 years old and greater.

Rectal supports A1, A2, B, and C with no restrictions.

A data set is defined as 3 predictive (adjusted) mode test temperatures and a 3-minute (oral or rectal) or a 5-minute (adult/pediatric axillary) monitor (Direct) mode reference temperature.

For febrile subjects less than 5 years of age only one predictive (adjusted) mode measurement may be taken if the child is unable to tolerate an additional 2 predictive (adjusted) mode measurements. This will be at the discretion of the clinician doing the temperatures if the child is not able to tolerate the 2 additional predictive temperature measurements.

IV. Informed Consent

Documentation of Informed Consent is requested for all subjects participating in this study per 21 CFR 50.27(a) and ICH E6(R2) 4.8.

> *Except as provided in § 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy shall be given to the person signing the form.*

A copy of the Informed Consent document will be available to all participants for review and, if agreed upon, the study subject or legally authorized representative (LAR) will sign the IRB/IEC approved informed consent. The subject or LAR will be given a copy of the signed consent to keep for their records. They will be informed by the study staff that their participation is voluntary. They may withdraw their participation at any time for any reason without loss of benefits to which they would be entitled.

The Principal Investigator (PI), or an authorized representative, will be responsible for reviewing the informed consent document with the study subjects and LAR, answering all questions, and obtaining a signed informed consent for all participants.

V. Study Population

A. Study Subject Demographics

Subjects may be recruited and enrolled from inpatient and outpatient acute care hospitals and clinics or research facilities. Subjects recruited to participate in this study may range in age from normal weight (full-term) newborns to adults. The subject may be anyone who is willing to have their temperature taken who also meets the eligibility criteria. Study subjects may have normal or febrile temperatures.

Study subjects may only be enrolled once per anatomical site.

A single subject may be enrolled in the oral, and/or axillary, and/or rectal site.

B. Expected Time Requirements

External Data Collection

The Study Subject commitment time may last approximately 20-30 minutes per anatomical site.

The data collected in this study will be collected by clinicians or researchers at the approved medical site who have been trained by the Primary Investigator.

Testing may last up to two years as it may be iterative in nature.

C. Subject Selection Criteria

Subject Inclusion Criteria

Study subjects (person who is having their temperature taken) must meet the following criteria to participate in this study:

- Subjects that are minors must provide assent according to the clinical site's policy (if approved by [redacted]) and/or the study sponsor's policy to participate in the study
- Subject or the legally authorized representative (LAR) must sign the informed consent form in order for the subject to participate.
- Subject must be willing and able to comply with the study procedures.
- Age: normal weight (full-term) newborn to adult
- The study subject is in ambient temperature for at least 20 minutes prior to participating.
- The study subject is able to have their temperature taken for up to six minutes for multiple rounds of temperatures per anatomical site.
- The study subject is not physically or emotionally agitated/uncooperative.
- The study subject or legal guardian speaks/understands fluent English.

Subject Exclusion Criteria

Study subjects (person who is having their temperature taken) are excluded if they meet any of the criteria below. Any subject that withdraws from the study will be replaced.

- The study subject has anatomical abnormalities that would affect temperature.
- The study subject has any known contraindication to oral, axillary, or rectal temperature measurements.
- The subject is not alert or unable to follow simple commands such as closing one's mouth completely around the probe if an oral reference temperature is being taken.
- The study subject has consumed food or drink, or smoked, within the last 20 minutes. The subject may be included if they wait 20 minutes prior to taking oral temperature.
- The study subject has engaged in strenuous or semi-strenuous activity within the last twenty minutes (i.e., running, weightlifting, etc.).
- Subject has taken antipyretics (Aspirin, acetaminophen, ibuprofen) in the preceding 120 minutes.

- Subjects have medical conditions such as inflammation at the MEASURING SITE (Barbiturates, thyroid preparations, antipsychotics, recent immunizations).
- Neutropenic immunocompromised patients, in whom rectal manipulation may seed the blood with bacteria.

Note: The study subject will be excluded if the reference temperature does not stabilize after the 3 -5 minute monitoring time.

VI. Subject Confidentiality

All subject data will be kept confidential and provided to the Welch Allyn study team members for algorithm validation only. Study data may be submitted to regulatory authorities and the IRB of record, if requested. A subject Screening/Enrollment Log will be utilized to assign all subjects with a subject identification number to be used to complete data forms.

VII. Subject Remuneration

Study participants will be compensated for their time and effort through an agreement with the study site.

[redacted]

VIII. Study Procedures

A. Informed Consent and HIPAA Authorization

Prior to performing any study related procedures all study subject volunteers, or their legally authorized representative, will provide written consent after study procedures have been explained in detail by authorized personnel trained by the study team. A copy of the informed consent will be available for review.

All participating study subjects will sign an informed consent document. Subjects will be informed that they may enroll in multiple groups (oral, axillary, rectal) which will be included in the informed consent.

The study details will be described in full by the Site Coordinator or other trained study personnel.

The investigator and/or his or her designee may conduct the IC process. The individual conducting the IC process shall be knowledgeable on how to conduct the IC process and of the study related procedures. If the study subject agrees to participate and signs the informed consent, a copy will be provided for their records.

Health Insurance Portability and Accountability Act (HIPAA) authorization is required as general health information will be obtained from the subjects.

B. Data Collection

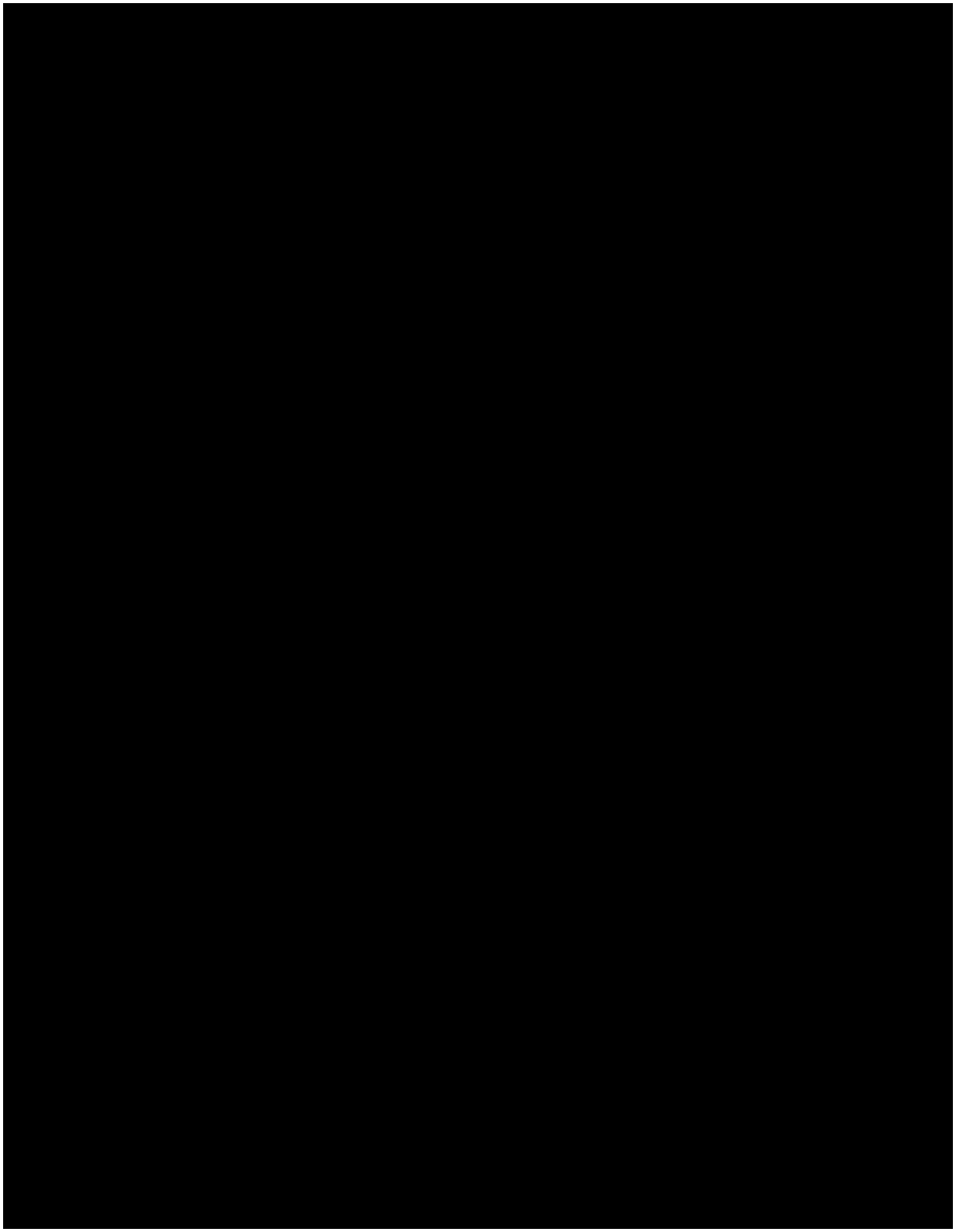
1. Screening / Enrollment Period

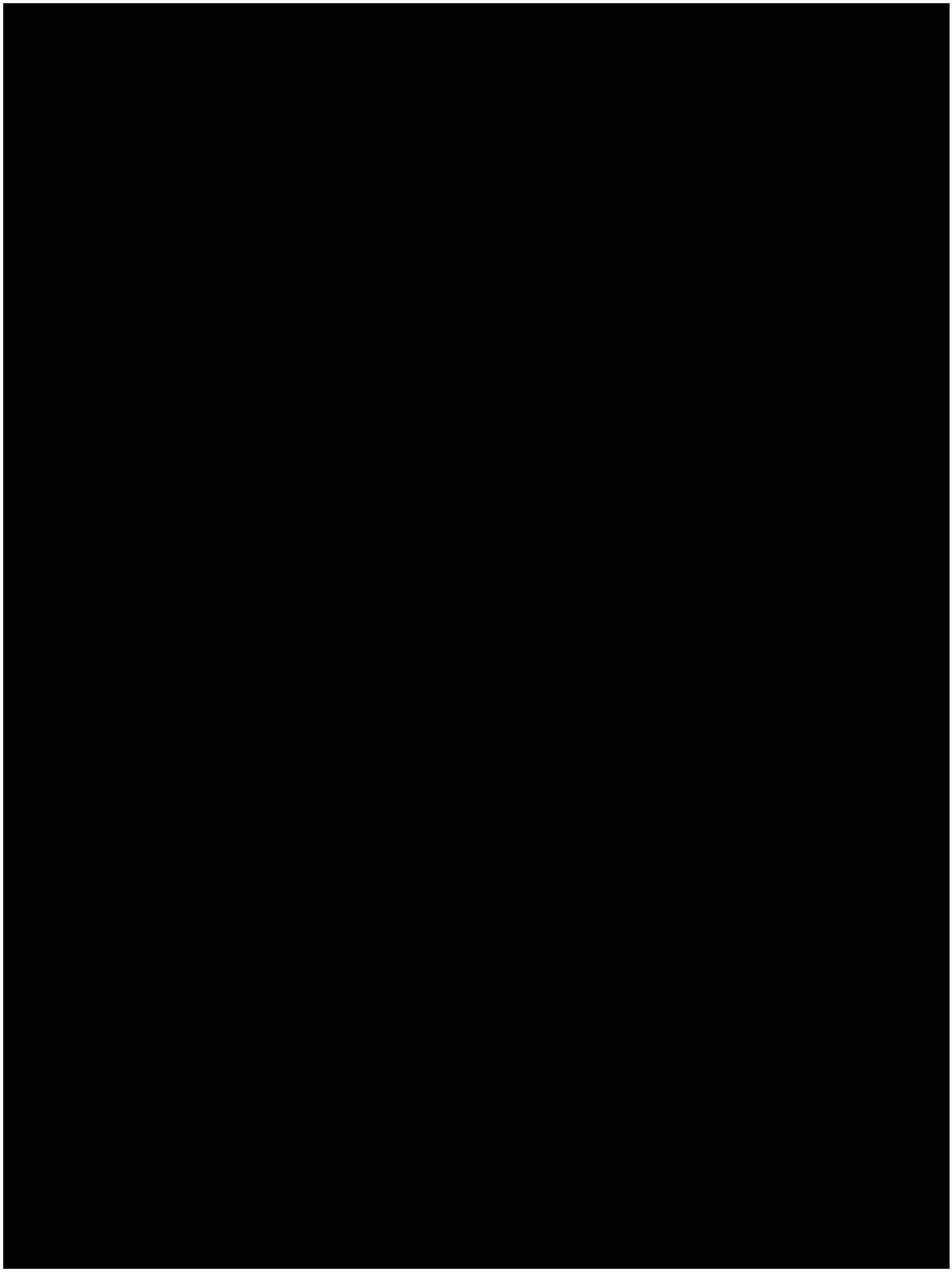
Subjects who meet inclusion/exclusion criteria and agree to participate by giving written informed consent will be enrolled in the study. The Study Subject Eligibility form in Appendix A will be used to determine whether the potential study subject meets the inclusion/exclusion criteria. If a subject chooses to participate in multiple temperature sites, this will be captured in the ICF, and they will use the same subject number on all data sheets completed. (one for each measurement site).

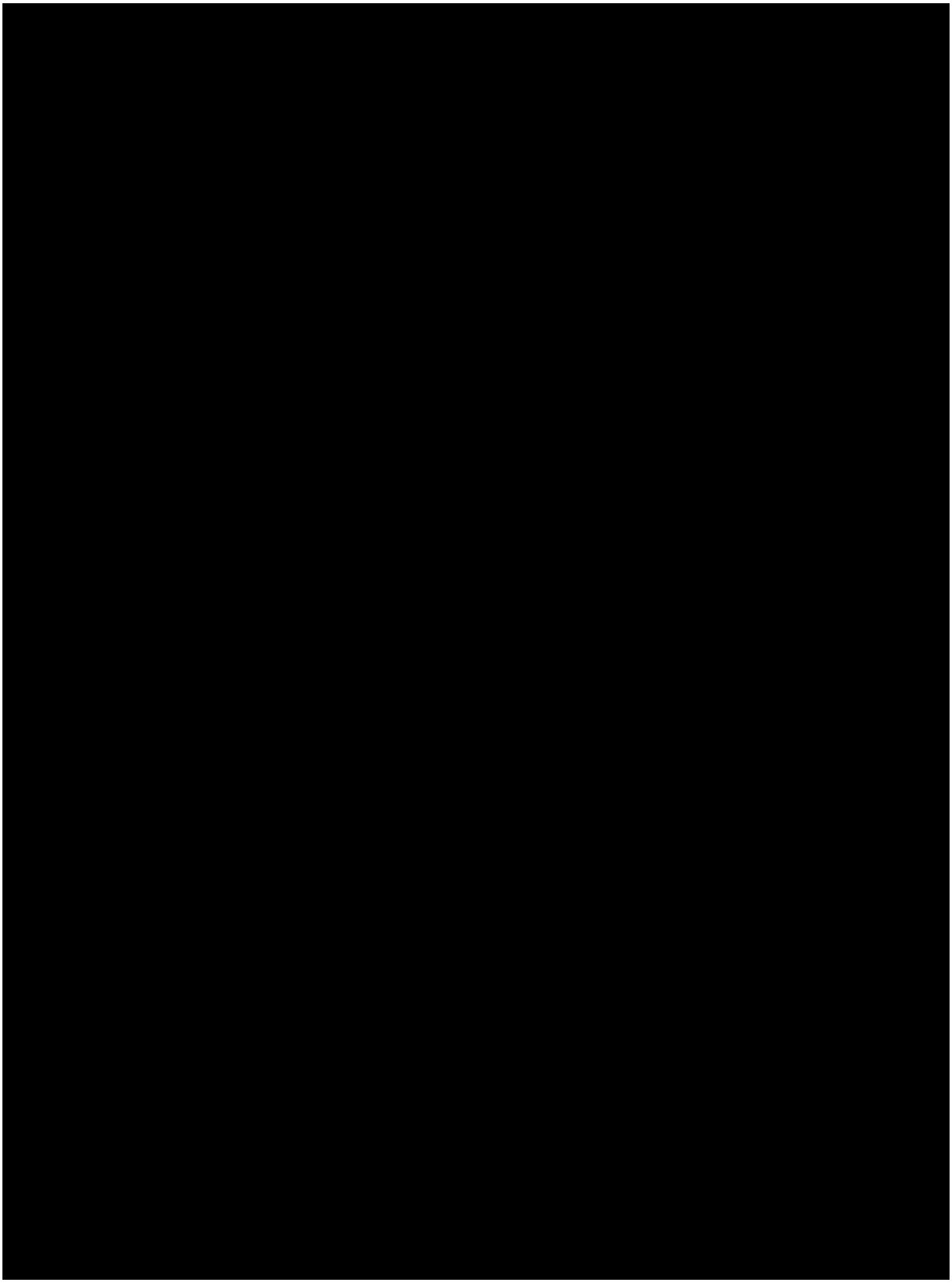
2. Data Collection

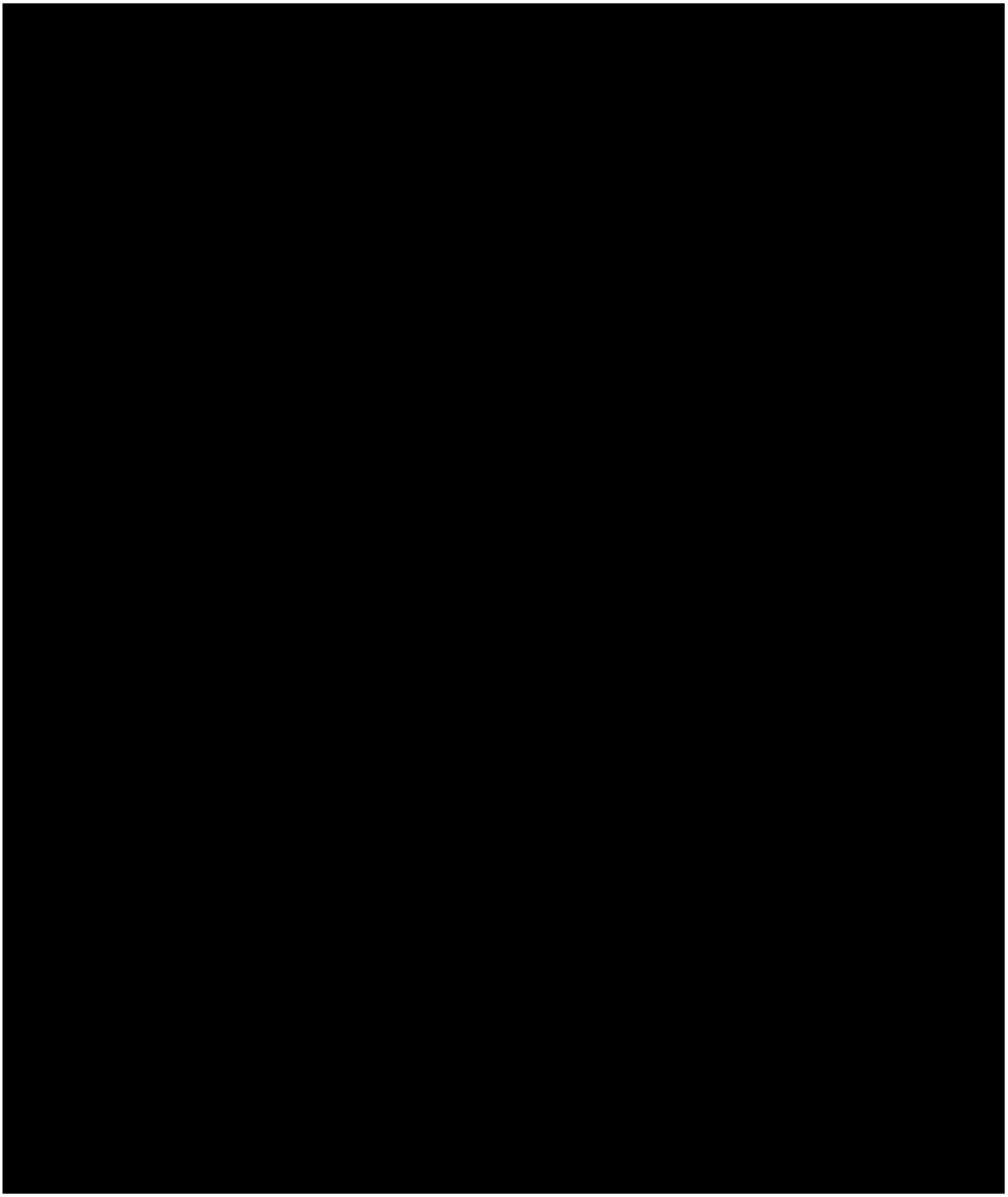
Research sites will collect the data sheets at the time of temperature data collection. The data will then be entered into the Electronic Data Capture (EDC) system within a timely manner.

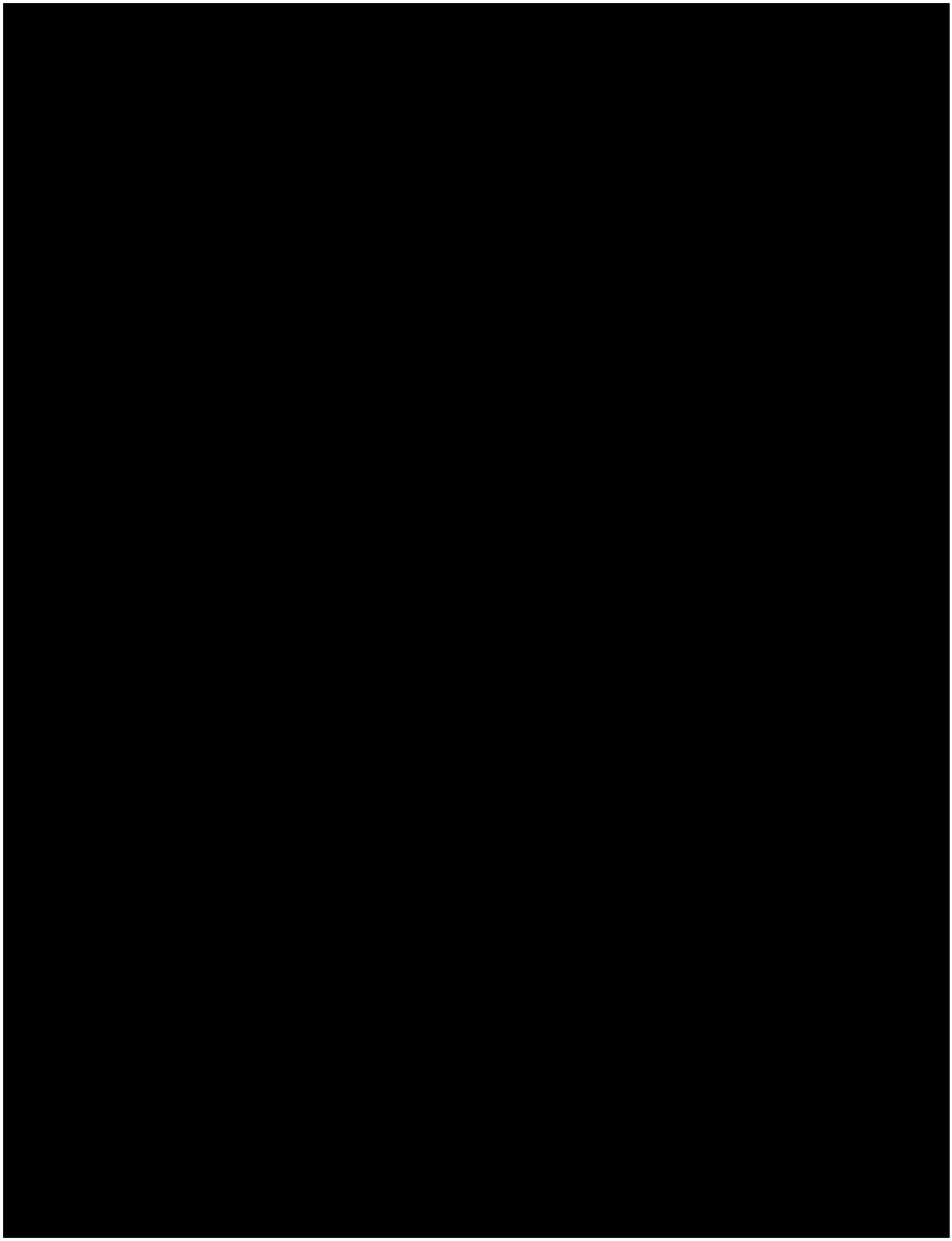
[redacted]











IX. Data Analysis and Reporting

A. Data Analysis

To evaluate the CLINICAL BIAS for the OPERATING MODE being evaluated, use the first CLINICAL THERMOMETER under test (DUT) OUTPUT TEMPERATURE out of three and the corresponding RCT (Reference Clinical Thermometer) OUTPUT TEMPERATURE from each subject in a test group. The CLINICAL BIAS for the specified REFERENCE BODY SITE and age group is calculated from Formula (2)

$$\Delta_{cb} = \frac{\sum_{i=1}^{n}\left(T_{DUT,i} - T_{RCT,i}\right)}{n} \quad (2)$$

where

i is the index number for an individual subject;

n is the total number of subjects per MEASURING SITE and age group;

$T_{DUT,i}$ is the ith observed OUTPUT TEMPERATURE from the DUT;

$T_{RCT,i}$ is the ith observed OUTPUT TEMPERATURE from the RCT.

201.102.4 * LIMITS OF AGREEMENT calculation

To calculate the LIMITS OF AGREEMENT, L_A, use Formula (3).

$$L_A = 2 \times \sigma_{\Delta_{cb}} \quad (3)$$

where

$\sigma_{\Delta_{cb}}$ is calculated using Formula (4).

To calculate the deviation, $\sigma_{\Delta_{cb}}$, use the first measurement of the CLINICAL THERMOMETER under test (DUT) OUTPUT TEMPERATURE out of three measurements and the corresponding RCT OUTPUT TEMPERATURE of each subject for the OPERATING MODE being evaluated using Formula (4).

$$\sigma_{\Delta_{cb}} = \sqrt{\frac{\sum_{i=1}^{n}\left[\left(T_{DUT,i} - T_{RCT,i}\right) - \Delta_{cb}\right]^2}{n-1}} \quad (4)$$

where

i is the index number for an individual subject;

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n is the total number of subjects per MEASURING SITE and age group;

$T_{DUT,i}$ is the ith OUTPUT TEMPERATURE indicated by the DUT;

$T_{RCT,i}$ is the ith OUTPUT TEMPERATURE indicated by the RCT;

Δ_{cb} is the CLINICAL BIAS as calculated in Formula (2).

* CLINICAL REPEATABILITY calculation

An ADJUSTED MODE CLINICAL THERMOMETER that makes continuous estimates of the REFERENCE BODY SITE temperature shall be exempt from the requirements of this subclause.

CLINICAL REPEATABILITY, for a particular OPERATING MODE, is determined for the subject population of all age groups given in Table 201.102 combined. Febrile subjects less than 5 years of age may be excluded.

CLINICAL REPEATABILITY is calculated by a pooled standard deviation of triplicate measurements over the entire population of subjects. First, calculate the standard deviation, σ_j, of the three OUTPUT TEMPERATURE measurements ($T_{1,j}$, $T_{2,j}$ and $T_{3,j}$) for each subject j using Formula (5).

$$\sigma_{j=}\sqrt{\frac{\sum_{i=1}^{m}\left(T_{\mathrm{DUT},i}-\overline{T_{\mathrm{DUT},j}}\right)^2}{m-1}} \qquad (5)$$

where

$T_{\mathrm{DUT},i}$ is the ith OUTPUT TEMPERATURE (e.g. 1, 2 or 3) indicated by the DUT;

$\overline{T_{\mathrm{DUT},j}}$ is the average of the OUTPUT TEMPERATURES on subject j;

m is the number of OUTPUT TEMPERATURE measurements on the subject.

NOTE m is typically equal to 3.

Then calculate a pooled standard deviation (the CLINICAL REPEATABILITY), σ_r, for all subjects using Formula (6).

$$\sigma_r = \sqrt{\frac{\sigma_1^2+\sigma_2^2+\ldots+\sigma_j^2+\ldots.+\sigma_N^2}{N}} \qquad (6)$$

where

N is the total number of subjects of all age groups in a study.

Definitions:

Clinical Accuracy: closeness of agreement between the output temperature of a clinical thermometer and the true value of the temperature of the reference body site that the clinical thermometer purports to represent

Clinical Bias Δ_{cb} : mean difference between output temperatures of a clinical thermometer and a reference clinical thermometer for the intended reference body site with specified limits of agreement when measured from selected group of subjects

Clinical Repeatability σ_r : pooled standard deviation (over a selected group of subjects) of changes in multiple output temperatures taken from the same subject from the same measuring site with the same clinical thermometer by the same operator within a relatively short time

Limits of Agreement L_A: the magnitude of a potential disagreement between outputs of two clinical thermometers equal to double the standard deviation of output temperature differences when used on the same human subjects. Limits of agreement can also be described as clinical uncertainty

Monitor (Direct) Mode: operating mode of a clinical thermometer where the output temperature is an unadjusted temperature that represents the temperature of the measuring site to which the probe is coupled

Predictive (Adjusted) Mode: operating mode of a clinical thermometer where the output temperatures are determined by measuring the rate of change of the sensor's output and using that information to anticipate or predict the final equilibrium temperature for the site it is measuring.

A detailed description of the statistical analysis will be presented in the Statistical Analysis Plan.

B. Final Report

At the conclusion of the data collection and analysis, a report will be generated and filed.

X. Administration of the Study

A. Training of Investigator & Site Staff

The Study Monitor will ensure that the Investigator and study site personnel have understood all requirements of the protocol and his/her regulatory responsibilities as an Investigator.

Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals such as a work instruction tool. In addition, the Study Monitor will be available for consultation with the Investigator and serve as the liaison for ISO 80601-2-56:2017 + A1 2018 between the study site and the Sponsor.

The Investigator is responsible for the conduct of all aspects of the study at the study site and verified by signature the integrity of all data transmitted to the responsible party. Whenever the term 'investigator' is noted in the protocol text, it may refer to either the Principal Investigator (PI) at the site, or an appropriately qualified, trained, and delegated individual of the investigational site. Sub-investigators or other authorized study personnel are eligible to sign for the Investigator, except where the Investigator's signature is specifically required. No additional clinical training is needed for the use of the investigational device.

B. Study Monitoring

Once the clinical site begins to screen and enroll subjects that are willing to participate, the site will also be responsible for data collection. A subject will be considered enrolled in the study after the signing of the ICF and confirmation of compliance with the inclusion/exclusion criteria. Subject compliance will be confirmed as all subjects will have their temperature measurements done with the provider in attendance during the entire measurement period.

All study personnel involved in this study will sign the Study Personnel Log and Site Training document.

The Sponsor team or designee will monitor the study data on site and remotely as part of safety management and clinical monitoring. Monitoring will occur at regularly scheduled intervals at the study site or remotely (e.g., videoconferencing) to allow for verification by sampling of source documents and comparing these with information recorded on the eCRFs in EDC. In addition, eCRFs will also be monitored remotely during the course of study participation.

The PI or a designated member of the PI's staff must be available at some time during monitoring visits to review data and resolve any queries and to allow direct access to the subject's records (e.g., medical records, office charts, hospital charts, and study-related charts) for source data verification. The eCRFs must be completed prior to each visit and be made available to the monitor so that their accuracy and completeness may be checked. Refer to the Clinical Operations Plan (or equivalent) for further details.

The sponsor will be responsible for training the clinicians on the devices and reviewing the protocol, monitoring the site, and verifying that the site is following [redacted] for study monitoring in accordance with Good Clinical Practice (GCP) recommendations and FDA regulatory requirements.

If the site is not meeting the minimum requirements to conduct the study or has administrative, procedural, or data quality deficiencies that require correction in order to comply with regulatory requirements, the protocol, or to meet the requirements of the sponsor, the site will be notified in writing of the deficiencies and permitted a reasonable opportunity to rectify deficient conditions. The inability of the site to rectify seriously deficient conditions in a timely manner or to maintain compliance with regulatory requirements may be the cause for termination of the study activities, closure of the investigational site, and notification of that decision to the relevant Institutional Review Board (IRB) and other regulatory authorities as appropriate.

The participating site will have an initial qualification visit by the sponsor, site initiation visit/training and routine interim monitoring in person site visits or via WebEx and/or phone calls by the sponsor during the study, and a study close-out meeting conducted by the sponsor. Additional monitoring meetings may be scheduled as needed.

Each monitoring meeting will utilize a standard checklist of elements to be reviewed at the site, tailored to the specific requirements of the study. Site monitoring visits will routinely review the participating site staff roster, study administrative and financial documents, required regulatory documentation, status of IRB approvals, changes or actions taken since any previous visit, participant recruitment status, documentation of informed consent for each participant, review of adverse events, investigational product storage conditions, outstanding data clarification, and a review of data elements against source documentation. Site visits follow standard Welch Allyn procedures, and a report will be prepared for study records.

C. Data Collection and Management

All clinical data associated with this study will be collected and reported electronically via a web address and secure password. The database will be housed on a physically and logically secure computer server maintained in accordance with written security policies. The Electronic Data Capture (EDC) system meets approved established standards for the security of health information and is validated per 21 CFR Part 11. The system also meets the ICH guideline E6R2 regarding electronic study data handling and is

available for audit upon request. Subject confidentiality will be strictly maintained. Subject identifying information will not be included in the database but must be maintained in a secure fashion at the Investigator site.

D. Maintenance of Study Records

All study related files must be maintained in a secure storage area to which only authorized personnel have access. Welch Allyn must maintain all Clinical Investigation Files for life of the product plus 15 years.

E. Risk/Safety Assessment

There are minimal risks to subjects, as described in Section I, C, Determination of Non-Significant Risk.

F. Anticipated Benefits to Subjects or Others

There are no direct benefits to subjects for taking part in this study. However, subjects may help Welch Allyn develop a new device to help benefit subjects in the future.

G. Adverse Events

Adverse Events (AEs) will be documented and reported per FDA requirements. AEs will be recorded on the Adverse Event Log and Adverse Event Form per procedure. The appropriate follow-up and safety measures will be completed and documented.

H. Device Deficiency Review

If a device deficiency (DD) is identified, it must be captured on the Unanticipated Problem eCRF in Rave/EDC and forwarded [redacted] without delay. Global Patient Safety MDV will provide DD assessment as appropriate and notify project manager or representative for investigation with follow-up if needed.

I. Unanticipated Adverse Device Effects

An Unanticipated Adverse Device Effect (UADE) is any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with, a device, to a subject if:

That effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or

Any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Welch Allyn must conduct an evaluation of any UADE and report the results of the evaluation to the FDA, IRB, and Investigator, within 10 working days after receipt of notice.

Where appropriate, Welch Allyn will review UADEs for potential impact on clinical test results.

J. Protocol Violations/Deviations

The Investigator will not deviate from this protocol without prior documented approval from the Sponsor and the IRB/IEC, except in cases of medical emergency. The Investigator may deviate

from the protocol without prior approval only when the change is necessary to eliminate an apparent immediate hazard to the patient. In that event, the Investigator will notify the Sponsor immediately by phone, notify the IRB/IEC and confirm notification to the Sponsor in writing as soon as possible, but within 5 working days after the change is implemented.

The investigator is responsible for recording deviations from the protocol in the CRF.

Protocol violations/deviations will be documented in source and in the Investigator's research study files as applicable. The clinical team will review deviations at a study level on a regular basis, as detailed in the Clinical Operations Plan (or equivalent).

K. Discontinuation of the Study

If a clinically significant safety finding is identified during the clinical study, the Investigator or the IRB may determine if any change in subject management is needed.

The Sponsor shall review AEs and assess risks during the conduct of a clinical investigation. The Sponsor shall terminate the clinical investigation if an unacceptable risk is confirmed. Decision to restart the study will be made jointly by Sponsor, the regulatory authority, the site-specific IRB, and the PI, following evaluation of the problems encountered.

The Investigator may terminate a subject's study participation at any time during the study if he/she judges it to be in the subject's best interest.

If a subject is withdrawn from the study, the study Monitor must be informed in the shortest possible time, regardless of the reason for withdrawal. In addition, a subject or the subject's legally authorized representative may discontinue his or her participation at any time during the study. If a subject's participation is discontinued, the reason(s) must be recorded in the source documents and on the CRFs.

If a subject is prematurely removed from the study, all data prior to discontinuation should be recorded in the CRF and all available data will be included in the statistical analyses.

XI. Financial Disclosure

[redacted]

APPENDIX A: Sample Study Subject Eligibility Form

[redacted] **Title:**	[redacted] **Protocol Number:**
Clinical Site:	**PI / Clinician:**
Informed Consent Date: __ __ ____ ____ ____ **Subject ID:** _____ _____ _____ _____ _____ _____ _____ _____ Y Y Y M M D D	

[redacted]

Inclusion Criteria (In order to include the subject in the study, all criteria should be checked **YES**.)	YES	NO
1. The subject is between the ages of normal weight (full-term) newborn to adult.		
2. The study subject is in ambient temperature for at least 20 minutes prior to participating		
3. The study subject is able to have their temperature taken for up to six minutes for multiple rounds of temperatures per anatomical site.		
4. The study subject is not physically or emotionally agitated/uncooperative.		
5. The study subject or legal guardian signs the ICF.		
6. The study subject or legal guardian speaks/understands fluent English		
7. The subjects that are minors must provide assent according to the clinical site's policy (if approved by Baxter) and/or the study sponsor to participate in the study.		
Exclusion Criteria (In order to include the subject in the study, all criteria should be checked **NO**.)	**YES**	**NO**
1. The study subject has anatomical abnormalities that would affect temperature		
2. The study subject has any known contraindication to oral, axillary, or rectal temperature measurements.		
3. The subject is not alert or unable to follow simple commands such as closing one's mouth completely around the probe if an oral reference temperature is being taken.		
4. The study subject has consumed food or drink, or smoked, within the last 20 minutes. The subject may be included if they wait 20 minutes prior to taking oral temperature.		
5. The study subject has engaged in strenuous or semi-strenuous activity within the last twenty minutes (i.e., Running, weightlifting, etc.)		
6. Subject has taken antipyretics (Aspirin, acetaminophen, ibuprofen) in the preceding 120 min		
7. Subject has medical conditions such as inflammation at the MEASURING SITE (Barbiturates, thyroid preparations, antipsychotics, recent immunizations)		
8. The study subject is neutropenic immunocompromised patient, in whom rectal manipulation may seed the blood with bacteria		

☐____ The subject meets all inclusion criteria and does not meet any of the exclusion criteria. Therefore, the subject is eligible to participate in the study.

☐____ The subject does not meet all inclusion criteria and/or meets at least one of the exclusion criteria. Therefore, the subject is not eligible to participate in the study.

PI / Clinician (Print): _____ Date: _____

PI / Clinician (Sign): _____

APPENDIX B: Sample Data Collection Form

[redacted] **Protocol Title:**	[redacted] **Protocol Number:**
Clinical Site:	**PI / Clinician:**

Subject ID Number: ___ ___ ___ ___ ___ ___ ___ ___ ___	**Subject Age:** _____ **Date:** _____
Devices: **CVSM S/N:** _____ **Software Version** _____	_____
Did the subject engage in strenuous or semi-strenuous activity within the last 20 minutes? ☐ **Yes** ☐ **No**	

TIMMY 3 algorithm temperature measurements

	(Please choose one and note laterality if appropriate) ☐ **TIMMY 3 algorithm-** ***3 Minute ORAL Monitor (Direct) Mode*** ***Sublingual Pocket* (L/R): _____** ☐ ***TIMMY 3* algorithm *3 Minute RECTAL Monitor (Direct) Mode*** ☐ ***TIMMY* 3 algorithm *5 Minute* Adult or Pediatric *AXILLARY Monitor (Direct) Mode* Axilla (L/R): _____	

First Predictive (Adjusted) Mode Reading		*Monitor (Direct) Mode Reading*		*Second Predictive (Adjusted) Mode Reading*		*Third Predictive (Adjusted) Mode Reading*	
Start Time		*Start Time*		*Start Time*		*Start Time*	
Stop Time		*Stop Time*		*Stop Time*			
Temperature (°C)		*Temperature (°C)*		*Temperature (°C)*		*Temperature (°C)*	

Note: *For febrile subjects less than 5 years of age only one predictive (adjusted) mode measurement may be taken if the child is unable to tolerate an additional 2 predictive (adjusted) mode measurements.* ***Febrile is defined as: Oral 37.5°C (99.5°F); Rectal 38.0°C (100.4°F); Axillary 37.2°C (99.0°F)***

PI / Clinician Name: _____

Signature: _____ Date: _____

APPENDIX C: Sample Recruitment Information

[redacted]

Objective: [redacted] is seeking subjects from (full term) newborn to adult to participate in a thermometer study.

- The study is collecting temperature in the mouth (oral) or under the arm (axillary) or in the rectum (rectal).
- We are looking for subjects without a fever or with a fever.
- Data collection (temperature measurements) will take approximately 20 minutes per site (oral, axillary, or rectal). Subjects can participate in one site like oral or all 3 if they meet the inclusion/exclusion criteria.

[redacted]

If you have any questions, please ask to speak to: _____