CLINICAL INVESTIGATION PLAN

Comparison of the mOm incubator with a standard incubator for the maintenance of thermal stability in infants (≤6kg)

Short Title: mOm Incubator Pilot Study

Sponsor CIP ref: mOm/2018/01
Version: 3.0, dated 09 March 2022

IRAS number: 224546

Clinicaltrials.gov: NCT03450668

This Clinical Investigation Plan (CIP) has regard for the Health Research Authority (HRA) guidance and order of content

SIGNATURE PAGE

The undersigned confirm that the following CIP has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved CIP and will adhere to the principles outlined in the Declaration of Helsinki, relevant Sponsor's Standard Operating Procedures (SOP)s and study specific procedures, the principles of Good Clinical Practice (GCP) and any other relevant regulatory requirements.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given. Any discrepancies from the study as planned in this protocol will be explained.

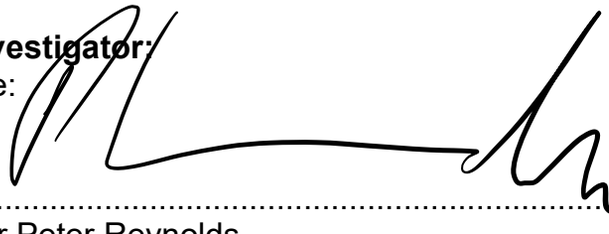
For and on behalf of the Study Sponsor:
Signature:

Date:
15 / 03 / 2022

.....
Name: Rosalyn Archer

Position: Director of Clinical Affairs, mOm Incubators Ltd

Chief Investigator:
Signature:



Date:
14 / 03 / 2022

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Name: Dr Peter Reynolds

Position: Neonatal Consultant, Ashford and St Peter's Hospitals NHS Foundation Trust

i. LIST OF CONTENTS

ii. KEY STUDY CONTACTS

Chief Investigator (CI) and Medical Expert	Dr Peter Reynolds, Neonatology Consultant, Ashford and St Peter's Hospitals NHS Foundation Trust, St Peter's Hospital, Guildford Rd, Lyne, Chertsey KT16 0PZ peter.reynolds1@.nhs.net 01932 723499
Study Co-ordinator (Project manager)	Rosalyn Archer, Director of Clinical Affairs, mOm Incubators Limited rarcher@momincubators.com 07853 633079
Sponsor	mOm Incubators Limited, Newstead House, Pelham Road, Nottingham, NG5 1AP www.momincubators.com
Funder	Sponsor funded: mOm Incubators Limited
Key Protocol Contributors	Dr Peter Reynolds and mOm Incubators Limited

iii. CLINICAL INVESTIGATION PLAN AMENDMENT HISTORY

Amendment No.	CIP Version No.	Date issued	Author(s) of changes	Details of Changes made
N/a	1.0	10 April 2018	Dr Peter Reynolds, Dr Isabel Reading (statistician) and Rosalyn Mazey	Original Clinical Investigation Plan
1	2.0	23 July 2021	Mariska Gulati	Title Updated Dates and staff role/details updated. Adverse event causality updated to MDR/MDCG guidance requirements.
2	3.0	09 March 2022	Mariska Gulati	Updated to clarify when recordings are required for each

				clinical data parameter and updated target recruitment period.

iv. STUDY SUMMARY

Study Title	Comparison of the mOm incubator with a standard incubator for the maintenance of thermal stability in infants (≤6kg)
Internal ref.	mOm/2018/01
Study Design	Prospective, multi-centred, randomised, controlled, cross-over study
Study Subjects	Babies at least 30 weeks Gestational age (GA) that are clinically stable but require at least 48 hours thermoregulated incubator care
Planned Size of Sample (if applicable)	36 completed subjects
Planned participation duration	48 hours per subject
Planned Study Period	Until recruitment is complete (target of nine months maximum recruitment period)
Research Question/Aim(s)	The study will compare the level of thermal care delivered to a clinically stable baby in the mOm incubator and a standard (non-humidified) incubator. Staff feedback on the experience of using the mOm incubator will also be collected.

v. ROLE OF SPONSOR AND INVESTIGATOR

Dr Peter Reynolds is the CI for this study and will be involved in all aspects of the study oversight. Both the CI and Principal Investigator (PI) at any other site(s) involved in the study are responsible for conduct of the study at their site and delegation of authority to appropriately qualified, and GCP trained, staff. This includes Sub/Co-investigators (SIs) (other consultants), research nurses (RNs) and any other members of the clinical research team. The CI and PI must complete a 'Delegation of Authority Log' detailing who may perform which study tasks including: gaining written informed consent from subjects' parents/legal guardians, recruitment, conduct of study data collection, completion / maintenance of study records and site files, and the final sign-off of each subject Case Report Form (CRF).

The investigators and Sponsor project manager are responsible for providing appropriate training for staff involved in the study and writing up the results of the study and management of their publication and appropriate dissemination.

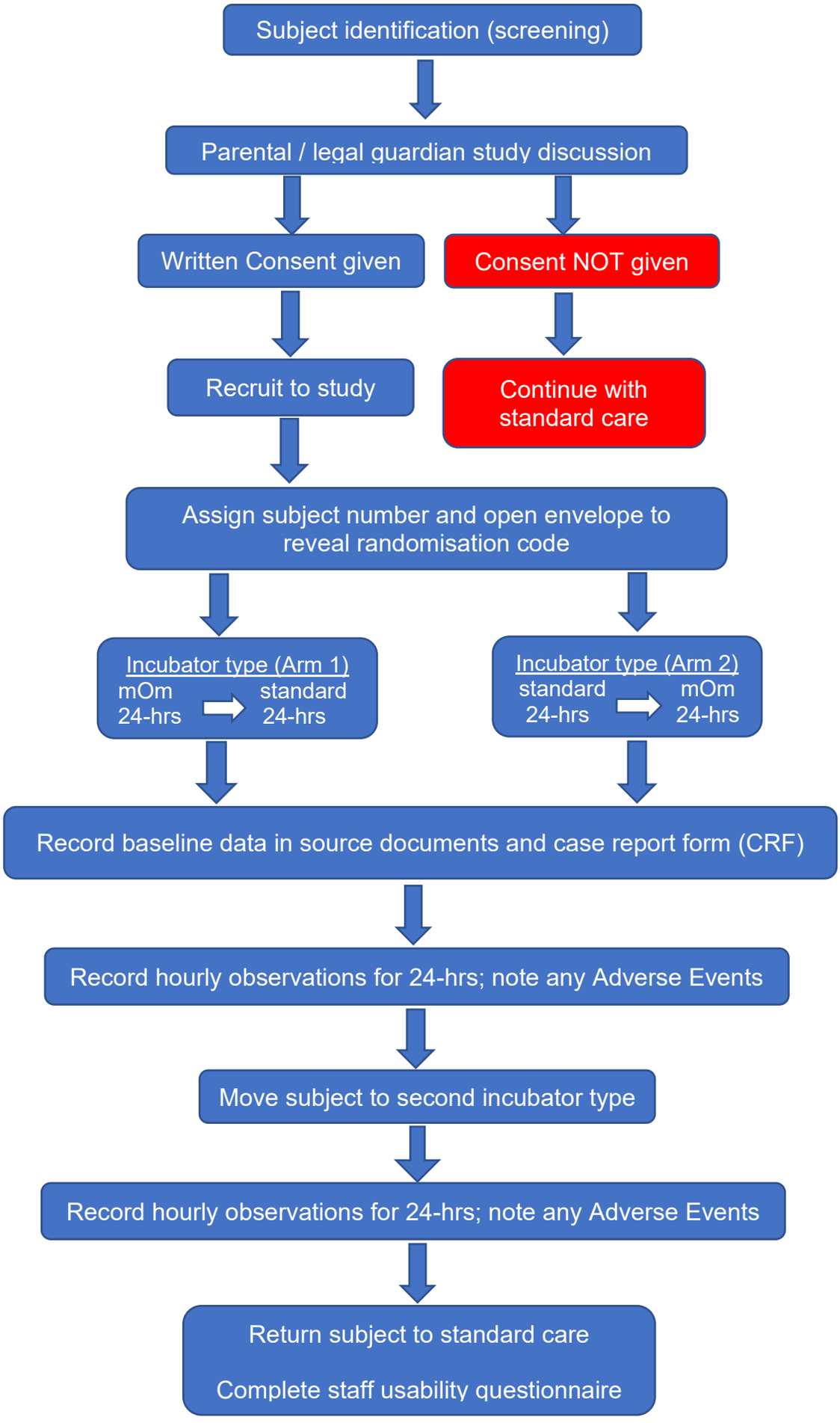
The Sponsor is funding the study, providing the mOm incubators, study management and data collection documentation and will be responsible for conducting source data verification (SDV) and checking site adherence to the CIP.

Dr Isabel Reading from the Faculty of Medicine at Southampton University, has provided statistical advice for this study.

vi. LIST OF ABBREVIATIONS

ADE	Adverse Device Event
AE	Adverse Event
CI	Chief Investigator
CIP	Clinical Investigation Plan
CRF	Case Report Form
GA	Gestational Age
GCP	Good Clinical Practice
GDPR	General Data Protection Regulations
GMP	Good Manufacturing Practice
HRA	Health Research Authority
IB	Investigator Brochure
ICF	Informed Consent Form
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
MHRA	Medicines and Healthcare products Regulatory Agency
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIS	Subject Information Sheet
REC	Research Ethics Committee
RN	Research Nurse
SADE	Serious Adverse Device Event
SAE	Serious Adverse Event
SDV	Source Data Verification
SI	Sub-Investigator (consultants working on the study with delegated responsibility from the PI/CI)
SOP	Standard Operating Procedure
TMF	Trial Master File

vii. STUDY FLOW CHART



1. BACKGROUND

Prematurely born infants are nursed in incubators to provide a stable and warm environment, until they can maintain a stable temperature in an open / warmed cot. It has been known for decades that hypothermia in the premature infant can cause cold stress resulting in poor weight gain and metabolic stress[1,2]. The baby maintains its normal temperature via hypothalamic control mechanisms, creating warmth (thermogenesis) through shivering and non-shivering mechanisms[3]. In the preterm or growth restricted baby, these mechanisms are less well developed, placing them at additional risk. In the developing world, hypothermia is associated with significant mortality especially in these higher risk patients[4].

1.1 Standard Practice

In the developed world, premature and growth restricted babies generally have access to sophisticated conventional incubators in hospital, which provide uniform and controlled temperature to minimise thermal stress. Generally, all babies born less than 1500g would normally be cared for in an incubator until they are able to regulate their temperature outside of a controlled environment; this cut-off varies between hospitals (*e.g*. 1400g at St Peter's hospital, London, but 1500g at St Mary's hospital, Manchester).

1.2 mOm Incubator

The mOm Incubator (trade name mOm Essential Incubator) is a infant incubator designed to provide a level of thermoregulation that meets the standards set for conventional incubators whilst being low cost and space-saving. James Roberts (CEO of mOm Incubators Limited) invented the mOm incubator after watching a documentary on Syria where he learned that, because of the stress of war, infant mortality rates have soared causing the country to lose nearly an entire generation to preventable infant deaths. The incubator design was part of his Design Engineering course at Loughborough University; he went on to win the Sir James Dyson Global Prize for Innovation in 2014.

2. RATIONALE

The mOm incubator fulfils the need to provide incubator care for babies requiring thermoregulation where standard incubators may not be available, such as in low to medium income countries.

This study aims to compare the ability of the mOm incubator to provide an adequate thermoregulated environment when used in a clinical setting using a prospective, multi-centre, randomised, cross-over study design to provide a direct comparison with standard incubators. It is hoped that the results of this study and the introduction of the mOm incubator could help to improve the survival rates of preterm babies born in places where access to expensive standard incubators is limited or not available.

The hypothesis is that the mOm incubator will perform as well as a standard incubator for routinely maintaining temperature stability in the baby.

2.1 Assessment of benefits / risks and management of risk

2.2.1 Benefits

The only direct benefit for subjects in this study is that the participating babies will be more closely observed than in standard care for babies fitting the inclusion criteria.

2.1.2 Risks and Management of Risk

The mOm incubator has been carefully designed to maintain a stable temperature environment for the baby.

The mOm infant incubator been manufactured under current Good Manufacturing Practice (GMP), designed and tested to provide a level of thermoregulation that meets the harmonised standards set for conventional baby incubators (BS EN 60601-2-19)[5,6]. More information and testing results for the mOm incubator will be provided to the site clinical research team in the form of an Investigator Brochure (IB). The clinical research team will have full control and responsibility for the baby's care and can withdraw a subject from the study at any time for any reason. The risks should therefore be no more than for standard routine incubator care.

If for any reason the subject, or incubator, has any unforeseen serious adverse event whilst the baby is in the mOm incubator the subject will immediately be removed from the study and placed into standard care. Monitoring of the serious adverse event will be followed up and if the adverse event is a serious device adverse event, the study will be halted with immediate effect and only be continued when the Sponsor and Chief Investigator are confident that the issue is resolved and will not be repeated.

If there are any concerns about temperature stability (or any other matter) in any baby being nursed in the mOm incubator during the study, then standard protocols for clinical evaluation by a doctor will be followed. At the discretion of the attending clinician, the baby can be moved into a conventional (standard) incubator at any time without restriction. A spare standard incubator will always be available for this purpose.

If there are unexpected clinical incidents such as Serious Adverse Device Events (SADE) these will be reported to the Sponsor, the Research Ethics Committee (REC), Medicines and Healthcare products Regulatory Agency (MHRA), NHS Trust Research and Development as well as through the normal NHS Trust Risk reporting mechanisms (Datix).

Photographs and/or video recordings of the use of the mOm incubator may be taken during the study but will be taken in such a way so that the baby cannot be identified. The study will adhere to the principles outlined in the Declaration of Helsinki[7], relevant Sponsor's SOPs and study- specific manuals included in the Investigator Site File (ISF) and Trial Master File (TMF), and, will follow the principles of GCP[8].

3. OBJECTIVES

3.1 Primary objective

The study will compare the level of thermal care delivered to a clinically stable baby in the mOm incubator and a standard (non-humidified) incubator.

3.2 Secondary objectives

Assessment of:

- Comparability to maintain clinical stability by measurement of physiological parameters.
- The mOm incubators ability to maintain and regulate its temperature to within the appropriate BS standard[5] in clinical practice.
- Comparison of between subject cleaning times.
- Incubator performance related adverse events.
- Staff feedback on the experience of using the mOm incubator (*i.e*. usability) will also be collected.

4. OUTCOME MEASURES

4.1 Primary Outcome Measure

Thermo-regulation ability of incubator to maintain stable core skin temperature of the baby over 24 hours.

4.2 Secondary Outcome Measures

4.2.1 Clinical stability:

- Pulse rate (Hourly)
- Respiratory rate (Hourly)
- Oxygen saturation (Hourly)
- Blood pressure (As per standard of care or at least once per day)
- Axiliary Temperature (As per standard of care, usually every 2-4 hours)

4.2.2 Temperature stability and regulation

Hourly record of temperatures displayed on the incubator:

- the actual incubator temperature
- set temperature of the incubator
- Core/truncal temperature (from vital signs monitor/skin probe)

4.2.3 Usability

Time to clean each incubator type between/after use.

4.2.4 Adverse events

ADE and SADEs assessed.

4.2.5 Staff feedback

All staff involved in the use of the incubator for care of the baby within, set up or cleaning will complete a questionnaire and provide any further anecdotal comments they wish to make.

5. STUDY DESIGN

The study has a prospective, multi-centre, randomised controlled, cross-over design. There will be two arms to the research. The first arm will consist of mOm incubator

care for 24 hours, followed by a further 24 hours where the subject is transferred for care to a standard incubator. The second arm will consist of 24 hours care in a standard incubator followed by 24 hours care in a mOm incubator. The care of the baby (subject) is mostly unchanged from standard incubator care, but observations may be recorded more frequently (*i.e.* hourly) for incubator displayed temperatures and some other physiological measures of clinical stability than would normally be collected in routine care for this type of clinically stable baby of at least 30 weeks GA (normally every three hours) (See Table 1). No additional blood tests or any other invasive testing or monitoring are required. The clinical research team will have full control and responsibility for the baby's care, with the ability to withdraw the baby from the study at any time for any reason if they feel the baby is clinically unstable or is adversely affected by their environment. The order of incubator type in which the baby is cared for (*i.e*. which arm of the study) before being crossed over to the alternative incubator type will be assigned at random at the point of written consent being gained and the subject therefore having been officially recruited.

Babies that are considered clinically stable from a cardio-respiratory point of view but require at least 48 hours incubator care but not requiring additional humidification will be recruited to the study from the Neonatal Unit. In practice, this will mostly be babies weighing less than approximately 1400g at 30 weeks, although some term babies may also be eligible for the study if they are being nursed in an incubator for clinical reasons.

The aim is to collect 36 completed data sets for analysis; to achieve this approximately 40 babies will be recruited; recruitment will be stopped once 36 completed data sets are available. The target is to complete recruitment within a nine-month period.

6. STUDY PROCEDURES

6.1 Recruitment

Identification and recruitment of subjects will be carried out by the attending Consultant Neonatologist and the clinical research team to whom responsibility has been delegated via the delegation of authority log.
Babies who are already being cared for in the Neonatal Unit, that meet the inclusion criteria for the study are eligible to be recruited as study subjects. For twins, consecutive enrolment will be possible if an appropriate incubator is available.

The parents/legal guardians of the baby(s) will be approached by a suitably qualified member of the clinical research team to provide written informed consent for their baby(s) to be recruited to this study. They will be given a Participant Information Sheet (PIS) to read and given the opportunity to discuss the study and ask any questions. It will be explained to them that allowing their baby to become a subject in the study is totally voluntary and if they do not agree to giving their consent, the standard care given will not be affected. If they do agree to let their baby become a subject in the study, they will be asked to sign an Informed Consent Form (ICF) of which they will be given a copy. Once written informed consent has been gained, the subject is registered on the enrolment log, considered recruited to the study and assigned a subject number.

6.2 Procedure

There will be two arms to the protocol as detailed in section 5. The Case Report Form labelled with the appropriate subject number contains the data forms for that subject and a randomisation envelope attached inside the cover of the CRF which indicates which incubator type (standard or mOm) will be used for the baby to spend the first 24 hours in, before being switched to the alternate incubator type for a further 24 hours.

All data collected for the duration of the study will be entered in the appropriate source data (*e.g*. medical notes, electronic data capture systems, cleaning logs *etc*) and into the subject's CRF. Adverse events (AE) should be entered.

Baseline data such as length, weight, gender, core/truncal temperature (recorded at time point 0 in physiological recordings section), GA at birth, date of birth and current age of the baby will be recorded on entry to the study. Hourly observations (+/- 15 minutes) will be taken throughout the following 48 hours of incubator care, and will include temperature data displayed on the incubator, plus routine clinical observations of the baby (*i.e.* pulse rate, O_2 saturation and respiration rate), plus axillary temperature as per standard practice and blood pressure recorded at least once per day (See Table 1 below)

Table 1: Clinical Data Recording

Parameter	**Frequency**
Core/Truncal Temperature	Hourly
Pulse Rate	Hourly
Oxygen Saturation	Hourly
Respiration Rate	Hourly
Axillary Temperature	As per standard of care (usually every 2-4hrs)
Blood Pressure	As per standard of care (at least once per day)
Events (*e.g*. door open for feeding, care, baby removed for cuddles)	For each event record start and end time, type of activity, number of portholes/door open, any error/alarms on the incubators and any comments.

Each incubator will be individually identified by serial number for reference in CRFs, source documents (medical record/chart) and on cleaning logs. The randomisation details and the identification number of the incubators used will be recorded when the subject put into the first incubator; likewise, at the 24 hours cross-over point.

Further details about the mOm incubator can be found in the Investigator brochure (IB) filed in the ISF. For the incubator, hourly temperature readings from the digital display, time to set up, time to clean, types of cleaning performed and reasons/times when incubator opened to administer to baby's care will be recorded.

Any unanticipated Adverse Events of the baby, or of the incubator functionality, or usability (*e.g*. malfunction or rainout), will also be recorded on the CRF, AE log in the ISF and in the patient notes.

In addition, the views of staff will be collected through completion of a questionnaire about the baby's comfort, visibility, ease of care, usability, ease to set up, ease of

cleaning and acceptability, one for each incubator type, per staff member involved in the study activities.

6.3 Inclusion / Exclusion Criteria

6.3.1 Inclusion criteria

The subject must satisfy all the following criteria to be eligible for the study:

- Parent/legal guardian is willing and able to give informed written consent for participation of their baby in the study.
- Parent/legal guardian is aged 16 years or above.
- Subject has spent at least a day (24 hours) in a standard incubator.
- Subject considered clinically stable from a cardio-respiratory point of view.
- Subject requires incubator care but does not require additional humidification.
- Subject requires incubator care for at least 48 hours.
- Subject is at least 30 weeks gestational age.
- Subject is less than or equal to 6kg in weight.

6.3.2 Exclusion Criteria

The subject may not enter the study if, in the opinion of the Investigator, or delegee taking consent, ANY of the following apply:

- Parent/legal guardian with learning disabilities or mental illness and is considered unable to give informed consent.
- Parent/legal guardian is a prisoner and young offender.
- Parent/legal guardian is considered to have a particularly dependent relationship with the investigator(s).
- Parent/legal guardian is deemed to belong to a vulnerable group.
- Subject has major congenital abnormalities.
- Subject has temperature instability, defined as being outside of a normal range based on each infant's individual characteristics.
- Attending clinician and/or nursing concern regarding clinical stability of the infant (*e.g*. infection suspected).

6.4 Withdrawal of Patients from the study

All subjects (via their parent/legal guardian) are free to withdraw from the study at any time for any reason without their standard of care being affected. If a patient is withdrawn before the completion of this study, the reason(s) for withdrawal will be documented where possible.

Withdrawal of a subject by a member of the clinical research team will occur for any of the following reasons:

- An unanticipated serious adverse event (*e.g*. SAE or SADE) which requires immediate change to alternative treatment.
- A protocol violation (*i.e*. violation of the inclusion/exclusion criteria during screening period or serious deviation from the clinical investigation plan, or guidelines during the study which may affect the integrity of the study or the patient's well-being).

7. ADVERSE EVENTS

7.1 Adverse event (AE)

Any undesirable clinical occurrence in a subject, whether considered to be procedure related or not, that includes a clinical sign or symptom. Typical AEs which should be recorded include but are not limited to: skin injury or infection, pressure sores, hyperthermia, hypothermia, apnea and brachycardia. AEs also include Adverse Device Events (ADEs). ADEs are any undesirable device related event, whether clinically relevant to the subject or not. Typical device ADEs which should be recorded include but are not limited to: rainout, practical access issues, degradation of part the incubator, inadvertent displacement of lines thought to be due to the design of the incubator.

AEs will be recorded from the time the subject has been enrolled and placed in the first incubator type until the end of their participation in the study (*i.e*. after 48 hours incubation is complete), unless a device related adverse event is on-going in which case it will be monitored until resolved. All AEs should be recorded in the patient notes, the CRF and on the Adverse Event log in the ISF. **7.2 Anticipated Adverse Event**

Any undesirable clinical occurrence in a subject that may be expected to occur during routine care. These will not be reported unless thought to be study related. Anticipated adverse events may include but are not limited to:

- Reflux
- Wind
- Nappy rash
- Crying

7.3 Serious Adverse Events

Serious Adverse Event (SAE) or **Serious Adverse Device Event (SADE)** any adverse medical or occurrence that:

1. Led to a death.

2. Led to a serious deterioration in health of a subject that:

    - Resulted a life-threatening illness or injury.
    - Resulted in a permanent impairment of body function or permanent damage to a body structure.
    - Resulted in an increased length of existing hospitalisation.
    - Resulted in requiring medical or surgical intervention to prevent permanent impairment of a body structure or a body function.

3. Might have led to death or a serious deterioration in health had suitable action or intervention not taken place.

7.4 Reporting of Adverse Events

All SAEs / SADEs must be reported by the Investigator to the Sponsor within 24 hours of learning of the incident, by the completion and emailing of an SAE report form, a copy of which will be available in the ISF. Notification of the SAE should be made by phone/email, then the SAE form emailed even if not entirely complete, within the 24-hour period of awareness.

The Sponsor will then liaise with the Chief Investigator and report the SAE to the REC, and the NHS Trust Risk reporting mechanisms (Datix). If deemed possibly device related, it will also be reported to the MHRA and the other PIs and SIs involved in the study.

All adverse events including AEs, ADEs, SAEs and SADEs which occur during the participation in the clinical study must also be recorded in the patient's notes and on the Adverse Event log within 10 working days and will be tracked by the Sponsor representative through regular site monitoring.

Severity of AEs must be identified. Table 2 provides definitions to be used to assess AEs.

TABLE 2: DEFINITIONS OF SEVERITY FOR ADVERSE EVENTS

Mild:	Symptom is only slightly noticeable to the subject or does not cause discomfort; does not negatively influence functioning; prescription drugs not required for relief of symptom but may be prescribed.
Moderate:	Symptom is of a sufficient severity to cause discomfort; performance of daily activities is negatively influenced; treatment for symptom may be needed.
Severe:	Symptom causes severe discomfort and incapacitation having significant impact on the subject's performance of daily activities; treatment for symptom may be given and/or subject's hospitalization may be extended.
Life Threatening:	An event that places the subject at immediate risk of death from the event.
Fatal:	An event that was the direct cause of the subject's death.

"Severe", "Life-Threatening" or "Fatal" AEs that are determined to be "causally related" to the procedure are to be reported to the Sponsor within 24 hours of the site's knowledge of the event (See definition in Table 3).

TABLE 3: DEFINITIONS OF RELATIONSHIP OF ADVERSE EVENTS

Not related:	Relationship to the device, comparator or procedures can be excluded when: • the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device • the serious adverse event does not follow a known response pattern to the medical device (if the response

	pattern is previously known) and is biologically implausible; • the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event; • the event involves a body-site or an organ that cannot be affected by the device or procedure; • the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); • the event does not depend on a false result given by the investigational device used for diagnosis9, when applicable; In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.
Possible:	The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
Probable:	The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

Causal Relationship:	The serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:
	
	• the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
	• the event has a temporal relationship with investigational device use/application or procedures;
	• the event involves a body-site or organ that
	  ○ the investigational device or procedures are applied to
	  ○ the investigational device or procedures have an effect on;

	• the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known); • the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible); • other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; • harm to the subject is due to error in use; • the event depends on a false result given by the investigational device used for diagnosis, when applicable; In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

8. STATISTICS AND DATA ANALYSIS

The primary endpoint is babies' truncal skin surface temperature variation; also termed core or central temperature. This is expected to fluctuate but remain within normal temperature limits (36.5 to 37.5 degrees Celsius). Variations from this endpoint will be analysed and compared statistically between the two arms of the study.

Thirty-six completed datasets are required for the analysis to be valid. A complete subject dataset will be deemed acceptable if 19 of the 24, once-hourly temperature observations have been recorded for each incubator type (*i.e.* 79% compliance). This degree of compliance was considered acceptable for analysis because it is still greater than the routine standard for this type of incubator care for clinically stable infants of 30 weeks GA or greater, which is often every three hours. Although data analysis will be largely descriptive, the performance of the mOm incubator will be statistically quantified by assessment of the fluctuations of babies' temperatures during each 24-hour period. It is expected that these babies' temperatures will fluctuate by around one degree Celsius, and this is normal. Thus, analysis will explore whether fluctuations for each baby keep within this bound. A 95% confidence interval will be calculated around the mean of these fluctuations within each baby for each of the two incubators. Data from 36 babies would allow such a confidence interval to be calculated to within plus or minus 0.33 of a degree if the actual mean fluctuations are around one degree (*i.e.* as normally expected) and assuming a two-sided confidence interval.

Each patient will serve as their own control. The order of incubator type used for each of the two consecutive 24-hour periods of incubator care, and therefore which study arm the subject is recruited to, will be assigned randomly. A Microsoft Excel random number generation system will be used to generate random numbers with which the arm of the study which the subject is to enter will be assigned. Each assignment will be placed in an envelope attached to each CRF already numbered with a continuous series subject number.

Baseline demographic factors of the study subjects will be summarised. For continuous variables, such as weight, the mean, standard deviation, median and range will be presented. For categorical variables, such as gender, the proportion of subjects in each category will be presented.

All data will be analysed based on intention-to-treat. Statistical analysis will focus on babies' temperature fluctuations whilst in each of the two incubators. Graphical displays of these, as well as summary statistics such as the variance of temperature throughout the two 24-hour periods will be presented. A 95% confidence interval for the size of these temperature fluctuations for each incubator type will be calculated and this measure will be used to consider whether the mOm incubator works as well as the standard one in maintaining temperature control. Secondary outcome measures will be presented similarly.

Questionnaire data will be summarised to assess usability and acceptability of the mOm incubator to the clinical research team (staff).

9. ETHICS

9.1 Declaration of Helsinki

This study will be conducted according to the guidelines established in the Declaration of Helsinki[7].

Subjects will be free to withdraw from the study at any time without prejudice to their subsequent treatment. In the instance of SADEs occurring the Sponsor and/or CI may decide to stop the study, with immediate effect, on grounds of patient safety at which point all subjects would move into the conventional standard care pathway.

9.2 Independent Ethics Committee Approval

This study will be conducted according to a favourable opinion from *[name to be inserted]* Research Ethics Committee (REC), the MHRA, Health Research Authority (HRA) and hospital NHS R&D governance committee.

9.3 Informed Consent

An appropriately trained member of the hospital registry study team, as indicated on the delegation of authority log by the CI/PI, will provide both written and verbal versions of the Participant information sheet (PIS) and Informed consent form (ICF) to the subject detailing no less than: the exact nature of the study; the implications and constraints of the CIP; and any risks involved in taking part. It will be clearly stated that the parent/legal guardian is free to withdraw the subject from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The subject will be allowed as much time as wished to consider the information, and the opportunity to question the Principal Investigator, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of subject dated signature and signature of the person who presented informed consent and only the investigator, or other appropriately trained person, identified by the CI/PI authorized to do so on the delegation of authority log. A copy of the signed Informed Consent will be given to the subject, a copy placed in their medical notes and a third copy retained at the study site with the case report form.

10. SUBJECT CONFIDENTIALITY

The Investigator will ensure that the subject's anonymity is maintained. Unique anonymous subject numbers will be the sole identifiers used, and no personal or non-anonymized data will leave the NHS Trust site. All documents will be stored securely and kept in strict confidence in compliance with the Data Protection Act 1998 and the new General Data Protection Regulations (GDPR), May 2018.

11. DATA MANAGEMENT

The only confidential data obtained for the study will be retained securely within the department in the approved study site in a designated folder (Investigator Site File).

The enrolment log will contain the subjects' name, hospital number, and date of birth, plus the date of consent and the allocated subject number which will identify the subject from then on. Standard procedures for handling and processing records will adhere to GCP and mOm Incubators Ltd SOPs.

11.1 Data Quality Assurance

Steps will be taken to ensure that the accuracy and reliability of data by the selection of qualified study sites, review of the study CIP procedures with the study site staff prior the study start, in addition to monitoring visits by a mOm Incubator Ltd representative (Project manager or appropriately trained CRA). All study related data will be reviewed for accuracy (where possible) and completeness and adherence to be CIP, as detailed in the monitoring plan. All identified discrepancies (protocol deviations) will be reported in the monitoring visit report, as a note to file in the ISF, discussed and resolved with the investigator or his/her delegated staff. A protocol deviation will be considered a protocol violation if it affects subject or public safety, or the integrity of the study. All protocol violations relating to public /subject health and safety will be reported to the REC and MHRA.

Persistent or serious non-compliance of an Investigator may require the Investigator to be disqualified from the Clinical Study.

11.2 Data Storage at the end of the study

All data removed from the study site(s) will be anonymized and will be retained such that it may be disseminated via publication for the public interest and for advancement of science as discussed in section 14. The confidential data would be retained at the end of the study for the period of time deemed suitable by the competent authority and specified within the standards governing clinical trials[9]. A certificate of destruction will be produced to confirm destruction. The records/data will be held for 15 years by the Sponsor and by each site according to hospital policy which can be 15 or 20 years. The exception is for data already published in the public domain which cannot be destroyed.

Data will be extracted manually from the medical notes and print outs from hospital based electronic systems and entered into an appropriately designed data collection form (CRF and study-specific logs). All personal data will be entered into a study specific database by the Sponsor where the data is to be analysed and held. Clinical data will be stored on a secure server with access restricted to appropriate personnel. Storage is on a restricted area of a file server. Authorization to access the restricted area of the file server is strictly limited. Data will be processed on a workstation by authorized staff. The workstations access the network via a log in name and password. Furthermore, all results are anonymized before analysis, and researchers will not be able to link specific results to individuals.

The study site Investigator will ensure that personal information is kept confidential. The NHS trust will be responsible for archiving the Investigator Site File including a copy of the CRFs for a period of 15 years. If they are moved from NHS Trust property or need to be destroyed beforehand this may be done only with written permission of the Sponsor.

12. FINANCING AND INSURANCE/INDEMNITY

The financing for the study will come from the Sponsor company, 'mOm Incubators Limited'. No payment will be made to study subjects. Appropriate insurance/indemnity will be provided by the Sponsor.

13. CLINICAL SUPPLIES

The Sponsor will supply all mOm incubators to be used in the clinical study and provide all necessary clinical study related documents such as, CRFs, staff questionnaires, study-related incubator cleaning logs and an Investigator Site File containing all of the other regulatory documents, study logs (screening, enrolment, delegation of authority and AE logs) which need completing, all study manuals, records of training and contracts, plus any other study related documentation.

The hospital will supply access to their standard incubators, routine incubator cleaning materials and standard source documents such as patient charts, monitor downloads, medical records.

14. REPORTING AND DISSEMINATION OF STUDY OUTCOMES

In the interests of science, salient positive or negative results shall be published in a manner that is timely, however allowing for the commercial progress of the company (*e.g.* sensitive to any patent filings or company proceedings). Information may be disseminated by means of journal publication, poster presentations, public databases (such as Clinicaltrials.gov), and presentations at conferences relevant to the fields of Neonatology, Medical Devices and Fetal Medicine.

Photographs/video recordings of the use of the mOm incubator taken during the study and data collected will be anonymized to prevent identification of the subject and photographs/video recordings will be taken in a way so that my baby cannot be identified. The data/photographs/video taken may be used for teaching of medical healthcare staff and students, both in the UK and abroad, and may be used in marketing materials (including online resources) which may be seen by the public. Although consent can be withdrawn from the study at any time, but photographs/video/data that have already been published cannot be withdrawn.

The Investigator may not publish or present study data without the written permission and review of the Sponsor.

15. REFERENCES

(1) Glass L, Silverman WA, Sinclair JC. Relationship of thermal environment and caloric intake to growth and resting metabolism in the late neonatal period. Biology of the Neonate 1969;13:324-40

(2) Hey EN, O'Connell B. Oxygen consumption and heat balance in the cot-nursed baby. Archives of Disease in Childhood 1970;45:335-43

(3) Knobel R, Holditch-Davis D. Thermoregulation and heat loss prevention after birth and during neonatal intensive-care unit stabilization of extremely low-birthweight infants. J Obstet Gynecol Neonatal Nurs. 2007 May-Jun; 36(3):280-7

(4) Lunze K, Hamer DH. Thermal protection of the newborn in resource-limited environments. J Perinatol. 2012 May; 32(5):317-24

(5) BS EN 60601-2-19. 2009+A1:2016. Medical Electric Equipment. Part 2-19: Particular requirements for the basic safety and essential performance of infant incubators (IEC 60601-2-19:2009). The British Standards Institutions 2017.

(6) BS EN ISO 10993-1. Biological Evaluation of Medical Devices. Part 1: Evaluation and Testing (ISO 10993-1:2003). June 2009, incorporating corrigendum April 2010.

(7) Declaration of Helsinki. Medical Research Involving Human Subjects. World Medical Association. Adopted 1964, amended 2013. 64th WMA General Assembly, Fortaleza, Brazil, October 2013

(8) BS EN ISO 14155:2011. Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice (ISO 14155:2011). BSI 2011.

(9) 2005/28/EC. Laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such product. Official Journal of the European Union, 8 April 2005.

(10) MDCG 2020-10/1 Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745.

16. INVESTIGATOR APPROVAL STATEMENT

TITLE: COMPARISON OF THE MOM INCUBATOR WITH A STANDARD INCUBATOR FOR THE MAINTENANCE OF THERMAL STABILITY IN INFANTS (≤6KG)

(ALSO KNOWN AS THE MOM INCUBATOR PILOT STUDY)

CIP REF: MOM/2018/01

VERSION 3.0, DATED 08 MARCH 2022

IRAS Ref: 224546

Clinicaltrials.gov: NCT03450668

I have read this Clinical Investigation Plan and agree to conduct this study as outlined within.

I acknowledge that it is my responsibility that all study staff members have read and understand all aspects of this Clinical Investigation Plan.

I agree to fully collaborate with mOm Incubators Limited during the conduct of this study.

I will adhere to this Clinical Investigation Plan, all applicable regulations and guidelines pertaining to clinical investigation of medical devices during as well as after completion of this study.

Investigator:

Printed Name: _____

Position: _____

Study Function: _____

Signature: _____

Date: _____