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BMJ Open

Evaluation of noninvasive continuous physiological monitoring devices for neonates in Nairobi, Kenya: A research protocol

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Complete List of Authors:	ginsburg, amy sarah; Save the Children Federation Inc Nkwopara, Evangelyn; Save the Children Federation Inc Macharia, William; The Aga Khan University, Paediatrics Ochieng, Roseline; Aga Khan University - Kenya, Faculty of Health Sciences Waiyego, Mary ; Pumwani Maternity Hospital Zhou, Guohai; Brigham and Women's Hospital Karasik, Roman; EarlySense Xu, Shuai; Sibel Inc.; Northwestern University Ansermino, J. Mark; The University of British Columbia
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1	Title: Evaluation of noninvasive continuous physiological monitoring devices for neonates in
2	Nairobi, Kenya: A research protocol
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5	Authors: Amy Sarah Ginsburg, ^{1*} Evangelyn Nkwopara, ¹ William Macharia, ² Roseline
6	Ochieng, ² Mary Waiyego, ³ Guohai Zhou, ⁴ Roman Karasik, ⁵ Shuai Xu, ^{6,7} and J. Mark
7	Ansermino ⁸
8	
9	
10	¹ Save the Children Federation, Inc., Fairfield, Connecticut, United States of America
11	² Aga Khan University, Nairobi, Kenya
12	³ Pumwani Maternity Hospital, Nairobi, Kenya
13	⁴ Brigham and Women's Hospital, Harvard Medical School, Boston, United States of America
14	⁵ EarlySense Ltd., Ramat-Gan, Israel
15	⁶ Sibel Inc., Evanston, Illinois, United States of America
16	⁷ Northwestern University, Evanston, Illinois, United States of America
17	⁸ The University of British Columbia, Vancouver, Canada
18	
19	

1			
2 3 4	20	* Corresponding aut	thor:
5 6 7 8	21	Mailing address:	Save the Children Federation Inc.,
9 10 11	22		501 King's Highway E, Suite 400
12 13 14	23		Fairfield, CT 06825, USA
15 16 17	24	Phone:	203.221.4000
21 22 23 24 25 26 27 28 29 30 31 32			
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4	26	ABSTRACT
5	27	
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, 8 9	28	Introduction: Continuous physiological monitoring devices are often not available for
10 11 12	29	monitoring high-risk neonates in low-resource settings. Easy-to-use, noninvasive,
12 13 14	30	multiparameter, continuous physiological monitoring devices could be instrumental in
15 16 17	31	providing appropriate care and improving outcomes for high-risk neonates in these low-
18 19	32	resource settings.
20		
21 22	33	Methods and Analysis: The purpose of this prospective, observational, facility-based
23 24 25	34	evaluation is to provide evidence to establish whether two existing noninvasive,
26 27	35	multiparameter, continuous physiological monitoring devices developed by device
28 29 30	36	developers, EarlySense and Sibel, can accurately and reliably measure vital signs in neonates
31 32	37	(when compared to verified reference devices). We will also assess the feasibility, usability
33 34 35	38	and acceptability of these devices for use in neonates in low-resource settings in Africa. Up
36 37	39	to 500 neonates are enrolled in two phases: 1) a verification and accuracy evaluation phase at
38 39 40	40	Aga Khan University - Nairobi; and 2) a clinical feasibility phase at Pumwani Maternity Hospital in
40 41 42	41	Nairobi, Kenya. Both quantitative and qualitative data are collected and analyzed. Agreement
43 44 45	42	between the investigational and reference devices is determined using a priori-defined
45 46 47	43	accuracy thresholds.
48 49 50	44	Discussion: We hypothesize that the investigational devices are equivalent to the reference
51 52	45	devices for each relevant measurement parameter of interest among neonates, and that the
53 54 55	46	investigational devices are feasible, usable and acceptable for use in neonates in low-
56 57 58 59 60	47	resource settings in Africa.

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3 4	48	Ethics and Dissemination: This trial was approved by the Aga Khan University Nairobi
5 6 7	49	Research Ethics Committee and the Western Institutional Review Board. We plan to
, 8 9 10	50	disseminate research results in peer-reviewed journals and international conferences.
10 11 12	51	ClinicalTrials.gov NCT03920761
13 14 15	52	
16 17	53	Keywords: neonates, continuous physiological monitoring devices
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STRENGTHS AND LIMITATIONS OF THIS STUDY

57		feasibility phase, and evaluation of two novel, investigational, noninvasive, multiparameter,
58		continuous physiological monitoring devices.
59	•	A verification of the reference devices is undertaken prior to initiating the accuracy
60		evaluation of the investigational devices to ensure the reference devices are robustly
61		functional and to confirm their within subject repeatability and accuracy compare to
62		standard clinical measurements for the relevant parameters of interest.
63	•	Reliability information gathered from the reference devices is utilized to determine
05	•	Reliability information gathered from the reference devices is dringed to determine
64		specific <i>a priori</i> Go/No Go criteria for each parameter and each investigational device.
65	•	As with all measurements, there is uncertainty inherent in the measurements from the
66		reference devices.
67	•	Inability to control for the characteristics and conditions of the participating neonates
68		and to standardize the environment and context are both strengths and limitations to
69		interpreting the results.
70		

• This research consists of two phases, a verification and accuracy evaluation phase and a clinical

1 2		
2 3 4 5	71	INTRODUCTION
6 7	72	In 2017 globally,
8 9 10	73	28 days of life, w
11 12	74	or 2.5 million nev
13 14 15	75	mortality with ar
16 17	76	African countries
18 19 20	77	Development Go
20 21 22	78	live births by 203
23 24	79	neonates will die
25 26 27	80	for early detection
28 29 30	81	reduce current a
31 32	82	Multiparameter
34 35	83	identifying neona
36 37	84	automatic interp
38 39 40	85	treatment is suff
41 42	86	devices would be
43 44 45	87	is greatest. While
46 47	88	settings, the devi
48 49 50	89	unsuitable for ap
51 52	90	to explore how t
53 54	91	settings. Ideally,
55 56 57	92	highly efficient ir
58 59	93	development of a
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2 3	94	African newborn or neonatal intensive care units that would allow these type of
4 5 6	95	technologies to be evaluated for feasibility and performance.
7 8 9	96	The Evaluation of Technologies for Neonates in Africa (ETNA) project was conceived with
10 11 12	97	the goal of advancing and supporting development, as well as evaluation, of select devices
13 14 15	98	for use in neonates. By establishing a testing platform in an African site, and working
16 17	99	collaboratively with partners with expertise in device development and evaluation and
18 19 20	100	neonatal and child health, the project seeks to boost development and optimization of
20 21 22	101	promising newborn care devices that could be applied in low-resource settings in Africa. The
23 24	102	purpose of this initial research is to produce evidence regarding the performance of two
25 26 27	103	existing noninvasive, multiparameter, continuous physiological monitoring devices
28 29	104	developed by device developers, EarlySense and Sibel. The intent is to provide evidence to
30 31 32	105	establish whether these investigational devices can accurately and reliably measure vital
33 34	106	signs in neonates (when compared to verified reference devices) and to assess the
35 36 27	107	feasibility, usability and acceptability of these devices for use in neonates in a low-resource
37 38 39	108	settings in Africa.
40 41 42 43	109	
44 45 46	110	METHODS AND ANALYSIS
47 48 49 50	111	Study design and setting
50 51 52	112	The primary objectives of this prospective, observational, facility-based research are: 1) to
54 55	113	assess agreement between repeat observations by the investigational device and the
56 57	114	reference device for each relevant measurement parameter of interest based on a priori-
58 59 60	115	determined accuracy threshold among neonates; 2) to compare clinical event detection

1		
2 3	116	performance between the investigational device and the reference device: and 2) to
4	110	performance between the investigational device and the reference device, and 5) to
5 6 7	117	determine whether the investigational device is feasible, usable and acceptable to hospital
8 9	118	administrators, healthcare providers (HCPs) and caregivers of neonates. Secondary objectives
10 11	119	include: 1) assessing diagnostic performance for each relevant measurement parameter of
12 13 14	120	interest based on sensitivity, specificity, positive predictive value, and negative predictive
15 16	121	value compared to the reference device; 2) determining the downtime performance of the
17 18 19	122	investigational device; 3) determining the alarm rate (events/hour) and the number of
20 21	123	true/false alarms of the investigational device compared to the reference device; 4)
22 23 24	124	determining the delay time between the investigational device and the reference device in
25 26	125	true events; and 5) determining the number of adverse device effects (ADEs) and serious
27 28 29	126	adverse events (SAEs) during use of the investigational device.
30 31	127	Taking place in Nairobi, Kenya, this research consists of two phases: 1) a verification and accuracy
32 33 34	128	evaluation phase conducted at Aga Khan University – Nairobi (AKU-N), a private, not-for-
35 36	129	profit university teaching hospital with a neonatal intensive care and high dependency units;
37 38 30	130	and 2) a clinical feasibility phase conducted at Pumwani Maternity Hospital (PMH), the largest
40 41	131	referral maternity hospital in sub-Saharan Africa with no neonatal intensive care or high
42 43	132	dependency units.
44 45 46	133	Study participants
47 48	134	Up to 500 neonates, corrected age of \geq 28 days admitted for routine observation and care at
49 50 51	135	AKU-N and PMH are recruited by trained study staff during routine intake and screening
52 53	136	procedures. To avoid potential selection bias, neonates are screened for enrollment in a
54 55 56	137	sequential manner, as much as possible. Trained study staff assess the neonate for all
57 58	138	inclusion and exclusion criteria (Table 1). Final eligibility determination is dependent on the
59 60	139	results of the medical history, clinical examination, appropriate understanding of the study

140	by the severity and completion of the unities informed concert process. A propose may
	by the caregiver, and completion of the written mormed consent process. A neonate may
141	be enrolled to the study more than once as long as they meet the eligibility criteria and the
142	caregiver(s) is willing to have the neonate participate.
143	For the feasibility, usability and acceptability assessment, hospital administrators and study
144	HCPs are enrolled if they are 18 years or older, involved in or aware of the ETNA study, and
145	have provided written informed consent. Caregivers may be enrolled if they are 18 years or
146	older, have a neonate enrolled in the study, and are willing to participate in a 30-minute in-
147	depth interview as well as direct observation while their neonate is on or attached to the
148	investigational device(s).
149	Investigational devices
150	Developed by Israeli-based EarlySense since 2009, the Insight system, released in 2016, is a
151	contact-free monitoring system comprised of a small piezoelectric sensor pad that can be
152	placed under the patient's mattress, and is designed to measure and record a patient's
153	heart rate (HR), respiratory rate (RR), motion, and sleep status. Information from the sensor
154	pad, in combination with EarlySense's artificial intelligence analytics, is transmitted to a
155	monitor to provide alert indications and vital sign trends to HCPs so that they can monitor
156	changes in a patient's condition. Currently in use in hospitals, rehabilitative centers, and
157	nursing homes to measure vital signs in adults and children above 10 kg, the device is
158	modified for use in neonates as part of this study. The adult device received regulatory
159	approval from the United States Federal Drug Administration (FDA) and has a Conformité
160	Européene (CE) mark for continuous and contactless measurement of HR, RR and motion.
161	No adverse events (AEs) related to the system have been reported during 10 years of
162	monitoring.
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2 3 4	163	Developed in 2019, the advanced neonatal epidermal (ANNE) system from Sibel, a
5 6 7	164	technology company spun out from the Center of Bio-Integrated Electronics at
7 8 9	165	Northwestern University in the United States, is a system of two time-linked soft and
10 11	166	flexible sensors designed to measure and monitor vital signs including HR, RR, oxygen
12 13 14	167	saturation (SpO ₂), and skin temperature in neonates. The chest sensor couples to the skin
15 16	168	via a hypo-allergenic, biocompatible hydrogel adhesive optimized for reduced peel force
17 18 19	169	upon removal, and the limb unit couples via a latex-free soft fabric wrap adaptable to a
20 21	170	range of foot sizes and anatomies. Information from the sensors are wirelessly transmitted
22 23 24	171	to a monitor or mobile device via encrypted Bluetooth™ for real-time streaming from a
24 25 26	172	customized mobile software application as well as onboard memory storage on the sensors
27 28	173	themselves. The device has been validated in more than 50 neonates in a neonatal care unit
29 30 31	174	without AEs.
32 33	175	Reference devices
32 33 34 35 36 37	175 176	Reference devices We are employing the Masimo Rad-97 [™] and the Spengler Tempo Easy Bleu devices as our
32 33 34 35 36 37 38 39	175 176 177	Reference devices We are employing the Masimo Rad-97 [™] and the Spengler Tempo Easy Bleu devices as our reference devices for this study. The Masimo Rad-97 [™] provides continuous physiological
32 33 34 35 36 37 38 39 40 41	175 176 177 178	Reference devices We are employing the Masimo Rad-97™ and the Spengler Tempo Easy Bleu devices as our reference devices for this study. The Masimo Rad-97™ provides continuous physiological monitoring of HR, RR, SpO2, and capnography. The Spengler Tempo Easy Bleu non-contact
32 33 34 35 36 37 38 39 40 41 42 43 44	175 176 177 178 179	Reference devices We are employing the Masimo Rad-97™ and the Spengler Tempo Easy Bleu devices as our reference devices for this study. The Masimo Rad-97™ provides continuous physiological monitoring of HR, RR, SpO2, and capnography. The Spengler Tempo Easy Bleu non-contact infrared thermometer predicts core body temperature from the temporal artery
32 33 34 35 36 37 38 39 40 41 42 43 44 45 46	175 176 177 178 179 180	Reference devices We are employing the Masimo Rad-97™ and the Spengler Tempo Easy Bleu devices as our reference devices for this study. The Masimo Rad-97™ provides continuous physiological monitoring of HR, RR, SpO2, and capnography. The Spengler Tempo Easy Bleu non-contact infrared thermometer predicts core body temperature from the temporal artery temperature.
32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50	175 176 177 178 179 180 181	Reference devices We are employing the Masimo Rad-97™ and the Spengler Tempo Easy Bleu devices as our reference devices for this study. The Masimo Rad-97™ provides continuous physiological monitoring of HR, RR, SpO2, and capnography. The Spengler Tempo Easy Bleu non-contact infrared thermometer predicts core body temperature from the temporal artery temperature. Study procedures
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32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58	175 176 177 178 179 180 181 182 183 184	Reference devices We are employing the Masimo Rad-97™ and the Spengler Tempo Easy Bleu devices as our reference devices for this study. The Masimo Rad-97™ provides continuous physiological monitoring of HR, RR, SpO2, and capnography. The Spengler Tempo Easy Bleu non-contact infrared thermometer predicts core body temperature from the temporal artery temperature. Study procedures Following completion of screening for eligibility, a study comprehension checklist, and written informed consent, study staff perform procedures according to the most recently approved version of the protocol (current version 1.1, June 18, 2019 (Appendix 1)). Enrolled

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188	Prior to initiating the accuracy evaluation of each investigational device, verification of the
189	reference devices, Masimo Rad-97™ and Tempo Easy Bleu, is undertaken at AKU-N to
190	ensure they are robustly functional and to confirm their within subject repeatability and
191	accuracy compared to standard clinical measurements for the relevant parameters of
192	interest. Neonates enrolled during reference device verification continue to receive local
193	standard of care while being observed intermittently for vital signs collection for a minimum
194	of 1 hour using the Masimo Rad-97™ and intermittent measurements with the Tempo Easy
195	Bleu. Observations may include video recordings of the neonate and the Masimo Rad-
196	97™reference device monitor for later review to facilitate manual count observations. The
197	reference device measurements will be compared to manual measurements, clinical
198	monitor observations, and video-assisted observations. Reliability information gathered
199	from the reference devices is utilized to determine specific Go/No Go criteria for each
200	parameter and each investigational device. Further evaluation of each investigational device
201	only proceeds should these criteria be met.
202	Encollment in the accuracy evaluation of the investigational devices. EarlySance Incight
202	Enroliment in the accuracy evaluation of the investigational devices, EarlySense insight
203	system and Sibel ANNE system, is initiated at AKU-N to formally assess their accuracy
204	compared to the verified reference device using repeated observations. Enrolled neonates
205	continue to receive local standard of care while having vital signs collected from the
206	reference device as well as one or both of the investigational devices. Placement of the
207	investigational and reference devices is done in a manner so as not to interfere with the
208	neonate's clinical care. Observations are collected for a minimum of 1 hour and potentially

demographic characteristics, current clinical status, medical history, medications; and a

physical examination is performed.

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2 3 4	209	for the entire duration of their stay in the hospital. Observations may consist of videotaping
5 6 7	210	and/or taking photos of the neonate during the observation period after obtaining informed
7 8 9	211	consent from the caregiver. During observation, clinical status and any activities are
10 11	212	updated and recorded including care activities (e.g., feeding, diaper changes, bathing,
12 13 14	213	kangaroo mother care, etc.), clinical procedures, interventions, therapies, laboratory tests,
15 16	214	medications, environmental features and exposures during hospitalization. The device
17 18 19	215	placement, output, and signal quality are also monitored. In addition, the neonates are
20 21	216	assessed for any safety issues. Agreement between the investigational and reference
22 23 24	217	devices is determined using a priori-defined accuracy thresholds. Thresholds are determined
25 26	218	based on the repeated observations performed on the reference device in the verification
27 28 29	219	phase, international standards, and clinical expert consensus opinion. Two a priori-
30 31	220	determined thresholds are determined: one lower threshold to allow the device developer
32 33 34	221	to optimize the device for retesting, and a second higher threshold to allow the device to
35 36	222	move on to the clinical feasibility phase of testing. A maximum of 5 rounds of testing and
37 38 30	223	retesting are permitted for each investigational device. Each round of testing or retesting
40 41	224	consists of using a cohort of 20 neonates. Should the lower threshold not be reached for at
42 43	225	least one parameter, no further testing of the investigational device is performed. Thus,
44 45 46	226	information collected during the accuracy evaluation along with the <i>a priori</i> -determined
47 48	227	Go/No Go criteria established during verification of the reference devices define which, if
49 50 51	228	any, of the investigational devices moves forward with additional rounds of testing or into
52 53	229	the clinical feasibility phase at PMH.
55 56	230	An investigational device advances to the clinical feasibility phase once the agreement for
57 58 59 60	231	the measurement parameters of interest exceed the higher accuracy threshold. Enrollment

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232	in the clinical feasibility phase of the investigational devices occurs at PMH in up to 120
233	enrolled neonates who receive local standard of care while being monitored with the
234	reference device(s) and one or both of the investigational devices. Observations are
235	collected for a minimum of 1 hour and involve measurement of vital signs via the
236	investigational and reference devices and monitoring for any critical event (i.e., low or high
237	HR, RR, or temperature or oxygen desaturation and apnea). Agreement between repeated
238	observations from the investigational and reference devices as well as diagnostic
239	performance in clinical event detection is evaluated. Additional performance metrics such as
240	alarm rates, alarm delays and uptime\downtime is compared between the investigational
241	and reference devices. Participation in the study does not interfere with or unnecessarily
242	delay the clinical care of the neonates.
243	Throughout all phases of the research, the investigational devices are not used to inform
244	clinical care. During the clinical feasibility phase, ETNA site study staff and hospital HCPs are
245	blinded to the data collected from the investigational devices to prevent interference with
246	clinical care. The study site investigators are responsible for close safety monitoring of all
247	participating neonates, including assessing for and reporting adverse device effects (e.g.,
248	erythema or edema at the investigational or reference device sensor site) and/or serious
249	adverse events (i.e., any adverse device effect resulting in permanent skin damage). Any
250	adverse device effects or serious adverse events will be treated until resolution or
251	stabilization, and may require removal of devices and withdrawal of the neonate from the
252	study if necessary.
253	Qualitative substudy

1 2		
2 3 4	254	After written informed consent is received from the qualitative study participants, a mixed
5 6 7	255	methods evaluation and data collection through audio-recorded semi-structured in-depth
, 8 9	256	interviews and direct observations are conducted by trained qualitative study staff to assess
10 11 12	257	the feasibility, usability, and acceptability of the investigational devices for monitoring of
12 13 14	258	neonates in an African-setting. All hospital administrators and study HCPs may be involved
15 16	259	in this portion of the study. Caregivers with a neonate enrolled in the study may also be
17 18 19	260	asked if they would like to participate in the qualitative portion of the study.
20 21	264	
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23 24 25	262	A total of up to 500 neonates are enrolled. For the verification of the reference devices at
26 27 28	263	AKU-N, up to 30 neonates are enrolled. Once this initial testing and data collection of the
29 30	264	reference devices is complete, for the accuracy evaluation phase at AKU-N, up to 120
31 32 33	265	neonates per investigational device are enrolled. For the clinical feasibility phase at PMH, up
34 35	266	to 120 neonates per investigational device are enrolled. The sample sizes for each phase
36 37	267	were selected to maximize the amount of information collected within the confines of the
39 40	268	available resources.
41 42 42	269	For the feasibility, usability, and acceptability assessment, the total sample size includes all
45 44 45	270	hospital administrators and study HCPs willing to participate and provide consent as well as
45 46	270	hospital administrators and study rice's wining to participate and provide consent as well as
47 48 49	271	up to 30 caregivers willing to participate and provide consent study at each site.
49 50 51 52	272	Data collection and quality assurance
53 54 55	273	Quantitative study data is collected by clinical study staff using designated source
56 57	274	documents as well as electronic or paper-based case report forms. Data is stored and
58 59 60	275	managed by a database developed via Research Electronic Data Capture (REDCap), a secure

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276	web application. Continuous physiological data and event data are recorded from the
277	investigational and reference devices at least once a second. All electronic data are collected
278	wirelessly or via a wired connection from the investigational and reference devices to a
279	study laptop using custom software applications. Qualitative study data is collected using
280	paper-based forms and audio recordings which are subsequently transcribed for analysis.
281	Clinical research data, including data collected from the investigational and reference
282	devices, are maintained through a combination of secure electronic data management
283	system and physical files with restricted access to ensure confidentiality. Two distinct study
284	databases are maintained separately: the primary study database and a database with
285	participating neonate's personally identifiable information. To ensure accuracy and
286	completeness, data is routinely reviewed by the sponsor through quality assurance reviews,
287	audits, and evaluation of the study safety and progress. Guideline for Good Clinical Practice
288	(GCP)/ ISO 14155 compliance is followed to ensure accurate, reliable, and consistent data
289	collection.
290	Data management
291	Primary data management activities, which include de-identified investigational and
292	reference device data transfer using end-to-end encryption with two-factor authentication,
293	data entry and validation, data cleaning, database quality control, and disaster recovery
294	plans are undertaken at the study site and are overseen by the on-site data manager. Data
295	review and analysis, oversight and preparation of final study database is performed by the
296	sponsor in collaboration with the study site. Data are maintained in databases hosted at the
297	study site. All data management activities are in compliance with International Council on

1 2		
2 3 4 5 6 7 8 9 10 11	298	Harmonization (ICH) GCP E6, sponsor organization, and institutional requirements for the
	299	protection of children and confidentiality of personal and health information.
	300	Outcomes
12 13	301	We hypothesize that the investigational device is accurate and reliable compared to the
14 15 16	302	reference device for each relevant measurement parameter of interest among neonates
17 18	303	and is feasible, usable and acceptable for use in neonates in low-resource settings. The
19 20 21	304	primary endpoint and secondary endpoints are detailed in Table 2.
21 22 23	305	Statistical analyses
24 25 26	306	Every second of data is automatically graded as optimal, acceptable and unacceptable based
27 28 29	307	on predefined rules for each device and each measurement parameter of interest according
30 31 32	308	to the quality of the data for each measurement parameter of interest. The Masimo Rad-
32 33 34	309	97™ provides a signal quality index that is used to determine data quality for HR and SpO2.
35 36	310	A custom algorithm has been produced to determine the capnography signal quality index.
37 38 39	311	Each of the investigational devices also provides a signal quality index. The quality
39 40 41	312	thresholds are determined following the verification phase. All comparisons are performed
42 43	313	from observations between two devices (or a single device during the verification phase). At
44 45 46	314	least 10 observations of 60 seconds of optimal quality data in each neonate, at least 5
47 48	315	minutes apart, are randomly selected for each measurement parameter of interest from the
48 49 50 51 52 53	316	full recording. For the clinical feasibility phase, accuracy comparisons use optimal or
	317	acceptable data. At least 3 hours of recording to a maximum of 12 hours are used for the
54 55 56 57	318	performance metrics such as alarm rates, alarm delays and uptime\downtime.
58 59 60		

1		
2 3 4	319	The repeatability of the reference device parameter estimates initially is assessed with the
5 6 7	320	intraclass correlation coefficient (ICC). Additional training or standardization of procedures
7 8 9 10 11 12	321	is performed to ensure at least good repeatability (ICC >0.7). This is followed by measuring
	322	agreement between the repeated reference observations and between the manual, clinical
13 14	323	monitor and video-assisted methods and the reference observations using the methods
15 16 17	324	described by Bland and Altman for replicated observations. ⁶ The agreement is reported as a
17 18 19	325	mean bias with 95% confidence intervals (Cis) and 95% limits of agreement. Graphical
20 21	326	representation of the data is assessed with agreement plots, Clark error grids, and Polar
22 23 24	327	plots to identify extreme outliers and significant data trends.
25 26 27	328	In the accuracy evaluation, the root mean square difference (RMSD) and ICC are calculated
28 29 20	329	for each measurement parameter of interest to compare the multiple repeated
31 32	330	observations between the investigational and reference devices. The agreement between
33 34 25	331	each investigational device and reference device(s) is then calculated using the methods
36 37	332	described by Bland and Altman for replicated observations. The agreement is reported as a
38 39	333	mean bias with 95% CIs and 95% limits of agreement. Graphical representation of the data is
40 41 42	334	be assessed with agreement plots, Clark error grids, and Polar plots to identify extreme
43 44	335	outliers, impact on clinical decisions, and significant data trends. An <i>a priori</i> -defined
45 46 47	336	accuracy margin for agreement is used as a threshold value to allow for decisions regarding
47 48 49 50 51 52	337	proceeding to additional testing.
	338	In the clinical feasibility phase, agreement between each investigational device and
53 54 55	339	reference device(s) is assessed as in the accuracy evaluation phase. Event detection rates,
56 57	340	alarm rates, alarm delays and uptime/ downtime are summarized with means, medians,
58 59 60	341	standard deviations and intra-quartile ranges as appropriate. Summaries of sensitivity,

2 3 4	342	specificity, positive predictive values and negative predictive values comparing each
5 6 7	343	measurement parameter of interest in the investigational device(s) to the reference
8 9	344	device(s) are produced. Comparisons of binary events are assessed using Cohen's weighted
10 11 12	345	Kappa and McNemar's test. The non-inferiority of alarm rates, alarm delays and uptime/
12 13 14	346	downtime are evaluated based on pre-specified thresholds.
16 17	347	Qualitative data are collected through in-depth interviews and/or semi-structured
18 19 20	348	questionnaires and analyzed to assess feasibility, usability, and acceptability of the
20 21 22	349	investigational devices among hospital administrators and HCPs, and acceptability among
23 24 25	350	caregivers of enrolled neonates. The qualitative data is in narrative format and the results
25 26 27	351	are descriptive. The questionnaires are coded and analyzed using a codebook with identified
28 29	352	themes, including feasibility of using each investigational device, barriers and facilitators to
30 31 32	353	use, and perceived value. Qualitative data analysis software is used to organize, code, and
33 34	354	analyze the qualitative data in an iterative process. The study team starts by identifying an
35 36 37	355	initial set of codes and themes based on the categories from the interview guides. During
38 39	356	the coding process, attention is paid to identifying emergent issues and themes that are
40 41 42	357	added to the codebook and included in the analysis. Responses from the interviews are
43 44	358	coded and discrepancies discussed and resolved for the final analysis and theme
45 46 47	359	identification.
48 49 50	360	
51 52 53	361	ETHICS AND DISSEMINATION
54 55 56 57	362	Ethical approvals and consent
58 59 60		

1 2		
2 3 4	363	The study is conducted in accordance with the ICH GCP and the Declaration of Helsinki 2008.
5 6 7	364	The protocol and other relevant study documents study were approved by the Western
8 9	365	Institutional Review Board (Puyallup, Washington, United States of America), and the Aga
10 11 12	366	Khan University Nairobi Research Ethics Committee (Nairobi, Kenya). Written informed
13 14	367	consent is obtained in the local language by trained study staff from all eligible neonate's
15 16 17	368	caregivers and for the qualitative substudy, from participating hospital administrators, HCPs,
17 18 19	369	and caregivers prior to enrollment.
20 21 22 23	370	Possible risks
24 25	371	Caregivers may feel compelled to enroll in the study in order to receive care for their
26 27 28	372	neonate within a research setting, which may be perceived as of a higher quality than the
29 30	373	standard of care. In order to minimize the risk of coercion, during the informed consent
31 32 33	374	process, study staff emphasize that the neonate will receive the required medical care
34 35	375	whether enrolled in the study or not. Other potential risks to study participation may
36 37 38	376	include those associated with the placement and attachment of the investigational and
39 40	377	reference devices, and delayed medical management. Study staff are trained in the
41 42 43	378	appropriate placement of investigational and reference devices' sensors to minimize
44 45	379	discomfort to the neonates as well as to avoid interference with any assessment, treatment,
46 47 48	380	or intervention necessary for clinical care. There is a potential risk of skin irritation with the
48 49 50	381	ANNE sensor system and neonates will be closely monitored and treated for any AEs. Study
51 52	382	staff are also trained in integrating study procedures with clinical care and to always
53 54 55	383	prioritize clinical care above study procedures. Extreme care is taken to ensure that no
56 57 58	384	necessary treatment is delayed to accommodate study procedures.
59 60	385	Dissemination

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3 4	386	We plan to disseminate study results in peer-reviewed journals and international
5 6 7	387	conferences, targeting those involved in the clinical care of neonates in low-resource
8 9	388	settings as well as those who develop and advise on policies and guidelines in those settings.
10 11 12	389	The trial is registered with ClinicalTrials.gov (registration number NCT03920761).
13 14 15	390	Efforts towards rigorous protocol
16 17 18	391	Dedicated study staff trained in GCP, operation, use and maintenance of the investigational
19 20	392	and reference devices, and study-specific procedures follow neonates enrolled in the trial to
21 22 23	393	assure the protocol and standard operating procedures are followed and data are accurately
24 25	394	collected. Standardized training, supervision, and oversight are undertaken to ensure
26 27 28	395	quality, consistency, and harmonized trial procedures and implementation. Regular
29 30	396	monitoring is provided by Save the Children to assess compliance with human subjects and
31 32 22	397	other research regulations and guidelines, adherence to the study protocol and procedures,
33 34 35 36	398	and quality and accuracy of data collected.
37 38 39	399	Limitations and bias
40 41 42	400	Limitations to this study and potential sources of bias include the sampling strategy, the
43 44	401	uncertainty inherent in the measurements from the reference devices, the limited
45 46 47	402	standardization of time of day of recording, and the inability to control the conditions and
47 48 49	403	standardize the context. Because there is a large variation in the various ages, weights, sizes,
50 51	404	disease states, clinical presentations, interventions received, and conditions of the
52 53 54	405	participating neonates, it is not possible to control for all these variables. Likewise, the
55 56	406	environment cannot be controlled, does not allow for complete standardization, and may
57 58 59 60	407	introduce additional sources of bias.

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408 **DECLARATIONS**

409 Authors' contributions ASG, EN, WM and MA designed the study and wrote the protocol. 410 RO, MW, GZ, and SX reviewed and provided critical input to the study design and protocol. ASG wrote the first draft of the manuscript, and EN and MA provided additional input. The 411 412 authors worked collaboratively and made the decision to submit the final manuscript for publication. 413 Acknowledgments We would like to thank Dustin Dunsmuir who wrote the IAP logger 414 application used to collect the high resolution data from the reference device. 415 Funding This work is supported by grants from the Bill & Melinda Gates Foundation 416 417 (OPP1203136) and the Save the Children Innovation Council. The authors had final responsibility for the decision to submit this manuscript for publication. 418 Competing interests RK is employed by EarlySense Ltd. and SX is employed by Sibel Inc. All 419 420 other authors declare that they have no competing interests. 421 Ethics approval and consent to participate The study was approved by the Western Institutional Review Board (Puyallup, Washington, United States of America) and the Aga 422 Khan University Nairobi Research Ethics Committee (Nairobi, Kenya). Written informed 423 consent is obtained by trained study staff from all eligible children's caregivers prior to 424 425 enrollment. **Consent for publication** Not applicable. 426 427 Patient and public involvement Patients and the public were not involved in the design of, 428 recruitment to, or the conduct of the study. Availability of data and materials Data will be made available on an open access platform 429

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3 4	430	after the publication of the main manuscripts. Processes will be developed to facilitate data
5 6	431	sharing for scientific utilization in a collaborative manner.
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7

TABLES AND FIGURE LEGENDS

Table 1. Eligibility criteria

Inclusion	• Male or female neonate, corrected age of ≥ 28 days.
criteria	Willingness and ability of neonate's caregiver to provide informe
	consent and to be available for follow-up for the planned duration
	of the study.
Exclusion	Receiving mechanical ventilation or continuous positive airway
criteria	pressure.
	• Skin abnormalities in the nasopharynx and/or oropharynx.
	Contraindication to application of skin sensors.
	Known arrhythmia.
	Presence of a congenital abnormality requiring major surgical
	intervention.
	• Any medical or psychosocial condition or circumstance that, in the
	opinion of the investigators, would interfere with the conduct of
	the study or for which study participation might jeopardize the
	neonate's health.

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Table 2. Study endpoints

Primary endpoints	
Agreement of the relevant measurement parameters of interest between th	ıe
investigational device and the reference device at each observation.	
Agreement of clinical event detection between the investigational device and th	ıe
reference device at each observation.	
 Feasibility, usability and acceptability of the investigational device amor 	۱g
hospital administrators and healthcare providers.	
 Acceptability of the investigational device among caregivers. 	
Secondary endpoints	
 Diagnostic performance of the investigational device to appropriately identify 	
the following critical events:	
the following critical events.	
 Low heart rate 	
 High heart rate 	
 Low respiratory rate 	
 High respiratory rate 	
 Oxygen desaturation 	
o Apnea	
 Low temperature 	
 High temperature 	
 Downtime duration of the investigational device. 	
Alarm rate (events/hour and ratio of false positives to missed critical events of	:
the investigational device's alarms compared to the reference device's alarms.	

2			
3 4		•	Response time of the investigational device's alarms compared to the reference
5			device's clarms for critical events
6 7			device's alarms for critical events.
8		•	Proportion of neonates with adverse device effects and serious adverse events
9 10			
11 12			resulting in skin damage.
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APPENDICES

455 Appendix I: Protocol, version 1.1, June 18, 2019

456 Appendix II: Schedule of study procedures and evaluations

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photographs					
Track clinical care and non-study			×	v	
activities					
Safety assessment			X		
End of study questions				X	
Removal of investigational and/or	O	K		v	
reference device(s)					
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Evaluation of Technologies for Neonates in Africa (ETNA) project

Full title: Evaluation of technologies for neonates in Africa

A Study of the Save the Children Technology Accelerator Unit Sponsored by:

Save the Children Federation, Inc., United States

Version 1.1 18 June 2019

Local Principal Investigator: William Macharia, MBChB,MMed, MSc Principal Investigators: Amy Ginsburg, MD, MPH and J. Mark Ansermino, MBBCh

Investigators	Investigators
Co-Investigator: Zvika Shinar	Co-investigator: Roseline Ochieng, MBChB, MMed
Co-Investigator: Shuai Xu, MD	Co-investigator: Mary Waiyego, MBChB,MMed

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, ETNA study staff, applicable regulatory authorities, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from Save the Children (or others, as applicable), unless it is necessary to obtain informed consent from potential ETNA study participants.

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Evaluation of Technologies for Neonates in Africa (ETNA) project

ABBREVIATIONS AND ACRONYMS

ADE	adverse device effect
AE	adverse event
AKU-N	Aga Khan University, Nairobi
ANNE	advanced neonatal epidermal system
CE	Conformité Européene
CI	confidence interval
CRF	case report form
CPAP	continuous positive airway pressure
EMC	electromagnetic compatibility
ETNA	Evaluation of Technologies for Neonates in Africa
FDA	United States Federal Drug Administration
GCP	good clinical practice
HCP	healthcare provider
HR	heart rate
ICC	intraclass correlation coefficient
ICF	informed consent form
ID	identification
IDI	in-depth interview
IEC	International Electrotechnical Commission
IRB	institutional review board
ISO	International Organization for Standardization
LAR	legally authorized representative
LRS	low-resource settings
nHDU	neonatal high dependency unit

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2		
3	NICU	neonatal intensive care unit
4 5	NSR	non-significant risk
6 7	PI	principal investigator
8	PMH	Pumwani Maternity Hospital
9 10	QC	quality control
11 12	RMSD	root mean square difference
13 14	RR	respiratory rate
15	SAE	serious adverse event
16 17	SCUS	Save the Children Federation Inc. United States
18 19	SDG	Sustainable Development Goal
20	300	
21 22	SOP	standard operating procedure(s)
22	SpO2	oxygen saturation
24 25	WIRB	Western Institutional Review Board
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PROTOCOL TEAM		
Principal Investigator (PI) and Medical Office Amy Ginsburg, MD, MPH	er:	
Senior Advisor, International Programs Save the Children Federation, Inc., United State Co-PIs: William Macharia, MBChB,MMed, MSc Aga Khan University, Nairobi, Kenya	PI signature es	Date
J. Mark Ansermino, MBBCh University of British Columbia, Canada		
Co-Investigators: Roseline Ochieng, MBChB, MMed Aga Khan University, Nairobi, Kenya		
Mary Waiyego, MBChB, MMed Aga Khan University, Nairobi, Kenya		
Zvika Shinar EarlySense		
Shuai Xu, MD Sonica		
Biostatistician: Guohai Zhou, PhD		
Research Manager: Evangelyn Nkwopara, MS		

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PARTICIPATING INSTITUTIONS AND CONTACT INFORMATION

Study Oversight/	Save the Children Federation, Inc., United States (SCUS)
Management:	501 Kings Highway Fast, Suite 400
Jenerageneen	Fairfield CT 06825
Medical Officer:	Amy Ginsburg MD MPH
	Save the Children Ecderation Inc. (SC)
	501 Kinga Highway East Suita 400
	SUT KINGS FIGHWAY EASI, SUILE 400
	+1-206-258-1827
	aginsburg@savechildren.org
Study Sites:	Aga Khan University Hospital, Nairobi (AKU-N)
	3rd Parklands Avenue, Limuru Road, Nairobi, Kenya
	Pumwani Maternity Hospital (PMH)
	Muratina Street Nairobi, Kenya
Study Operations:	Aga Khan University, Nairobi, Kenya
Local Collaborators:	Aga Khan University, Nairobi, Kenya
	Pumwani Maternity Hospital, Nairobi, Kenya
Statistical Support:	Guohai Zhou, PhD
Technical Support:	EarlySense
	US Office:
	800 West Cummings Park
	Suite 6400, Woburn, MA 01801 United States
	International Office:
	Derech Ze'ev Jabotinsky 7
	Ramat Gan 5252007 Israel
	Sonica
	1900 Greenwood Street Suite 2
	Evanston Illinois 60201 United States
	The Bill & Melinda Cates Foundation
r unung Agency.	500 Eifth Avenue North

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PROTOCOL OUTLINE

Title:	Evaluation of technologies for neonates in A	Africa		
Study Oversight and Management:	Save the Children Federation Inc., United S	tates		
Collaborating	Save the Children Federation Inc., United States (SCUS)			
Organizations:	Aga Khan University – Nairobi (AKU-N)			
	Pumwani Maternity Hospital (PMH)			
Funding Sources:	Bill & Melinda Gates Foundation			
Rationale:	Low-cost, operator-independent, efficient, non-invasive multiparameter continuous physiological monitoring devices are necessary for use and need			
	to be evaluated in neonates in a low resour	ce settings.		
Population:	Neonates at AKU-N and PMH			
Schema:	Up to 500 children total will be enrolled in the	ne following mar	nner:	
	Study phase N	EarlySense So	onica	
	Phase I: verification 20	N/A N/A	A	
	Phase I: accuracy evaluation 240*	120 120	0	
	Phase II: clinical feasibility 240	120 120	0	
	* 5 rounds of testing and retesting per investigational	levice, 20 neonates	s per round	
Objectives:	Primary:			
	 investigational device and the reference measurement parameter of interest inferiority margins among neonates. 2. To compare clinical event detection investigational device and the reference and acceptable among healthcare pand caregivers of neonates. 	nce device(s) fo based on <i>a prio</i> performance be nce device(s). ional device is fo roviders, hospita	or each relevant ri-determined non- etween the easible, usable al administrators,	
	Secondary:			
	1. To assess diagnostic performance for each relevant measurement parameter of interest based on sensitivity, specificity, positive predictive value, and negative predictive value compared to the reference device(s).			
	 To determine the downtime perform To determine the alarm rate (events) 	ance of the inve /hour) and the n	estigational device. number of true/false	
	alarms of the investigational device device(s).	compared to the	e reference	
	4. To determine the delay time betwee reference device(s) in true events.	n the investigati	onal device and the	
	5. To determine the number of adverse events resulting in skin damage dur	e device effects ng use of the in	and serious adverse vestigational device.	

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Endpoints:	Primary
	 Agreement of the relevant measurement parameters of interest between the investigational device and the reference device(s) at each observation. Agreement of clinical event detection between the investigational device and the reference device(s) at each observation. Feasibility, usability and acceptability of the investigational device among healthcare providers and hospital administrators. Acceptability of the investigational device among caregivers.
	Secondary
	 Diagnostic performance of the investigational device to appropriately identify the following critical events: a. Low heart rate b. High heart rate c. Low respiratory rate d. High respiratory rate e. Oxygen desaturation f. Apnea g. Low temperature Downtime duration of the investigational device. Alarm rate (events/hour) and ratio of false positives to missed critical events of the investigational device's alarms compared to the reference device(s)' alarms. Response time of the investigational device's alarms compared to the reference device(s)' alarms for critical events. Proportion of neonates with adverse device effects and serious
	adverse events resulting in skin damage.
Timeline:	Total project anticipated to take 18 months to complete.

1 INTRODUCTION

1.1 Background

In 2017 globally, 47% of all deaths in children under five years of age occurred within the first 28 days of life, which translates to a neonatal mortality rate of 18 deaths per 1000 live births.¹ Sub-Saharan Africa bears the greatest burden of neonatal mortality with an estimated 1 million newborn deaths in 2017.¹ Further efforts, especially in African countries, are needed to push progress towards achieving the Sustainable Development Goal (SDG) 3 target of reducing global neonatal mortality to 12 deaths per 1000 live births by 2030.² Innovations in neonatal care, particularly technologies that allow for early detection and intervention of major morbidities, hold great promise in helping to reduce current neonatal mortality rates.

Multiparameter continuous physiological monitoring devices could be instrumental in directing care provided for a neonate through automatic interpretations of vital signs that help identify critical events and determine if treatment is sufficient or insufficient, ultimately improving newborn outcomes.³⁻⁴ These devices would be most useful in low-resource settings (LRS) in sub-Saharan African were the need for such technologies is greatest. While such devices currently exist and are standard of care in high-resource settings, they are expensive and require specialized training to operate, making them unsuitable for application in LRS. To address these barriers, it is necessary to explore how these technologies can be adapted and/or optimized for use in LRS. Ideally the devices should be low cost, operator-independent, and highly efficient in diagnostic performance and operator workload. This requires development of a robust testing platform that appropriately mimics conditions common in an African newborn unit or neonatal intensive care unit (NICU) that would allow these type of technologies to be evaluated for performance and feasibility.

To this end, the Evaluation of Technologies for Neonates in Africa (ETNA) project was conceived with the goal of advancing and managing development, as well as evaluation, of select devices for use in neonates. By establishing a testing platform in an African site, and working collaboratively with partners with expertise in device development and evaluation and neonatal and child health, the project seeks to boost development and optimization of promising newborn care devices that could be applied in LRS in Africa.

1.2 Rationale

To further reduce neonatal mortality rate in LRS in Africa, research is needed to develop and optimize innovations in newborn care, specifically technologies that are low cost, operatorindependent, and highly efficient. The purpose of the ETNA project and this initial study is to produce information and data regarding the performance of two existing multiparameter continuous physiological monitoring devices developed by device developers, EarlySense and Sonica. The clinical trial described in this protocol is intended to provide evidence to establish whether these investigational devices can reliably and accurately measure vital signs in neonates (when compared to verified reference devices) and to assess the feasibility, usability and acceptability of these devices for use in neonates in a LRS in Africa.

1.3 Investigational Devices

1.3.1 EarlySense Insight System, EarlySense Ltd.

The EarlySense Insight system is a contact-free monitoring system, that measures and records a patient's vital signs and motion parameters. The system was developed by Israeli-based EarlySense. The system is comprised of a small piezoelectric sensor pad that can be placed under the patient's mattress to monitor heart rate (HR), respiratory rate (RR), patient motion, and sleep status. There is no physical contact between the sensor and the patient. Information from the sensor pad, in combination with EarlySense's artificial intelligence analytics, is transmitted to a monitor or mobile application to provide alert indications and vital sign trends to healthcare providers (HCPs) so that they can monitor changes in a patient's condition. These alert indications, together with EarlySense artificial intelligence capabilities are able to detect sepsis, respiratory depression, sleep apnea, and arrhythmias, among other conditions. This device is currently in use in hospitals, rehabilitative centers, and nursing homes to measure vital signs in children and adults above 10 kg but will be modified for use in neonates as part of

this study. The adult device received regulatory approval from the United States Federal Drug Administration (FDA) and has a Conformité Européene (CE) mark for continuous and contactless measurement of HR, RR and motion.

The EarlySense system has been subject to full verification and validation tests that include:

- 1. Risk analysis
- 2. Software verification and validation
- 3. Electromagnetic compatibility (EMC) and safety testing
- 4. Full load bench testing
- 5. Non clinical testing: EarlySense Insight performance verification

The electrical safety and electromagnetic compatibility of the EarlySense system (InSight and sensor) were tested by external laboratories to demonstrate that the system is compatible with the requirements of the International Electrotechnical Commission (IEC) 60601-1 and IEC 60601-1-2 standards. Risk analysis activities were performed in compliance with the requirements of International Organization for Standardization (ISO) 14971 "Application of risk management to medical devices." It was concluded that the potential risks of the EarlySense InSight system are minimal and acceptable. It is considered as a non-significant risk device (NSR). Hundreds of these systems have been installed in healthcare institutions (hospitals, long-term care and skilled nursing facilities) and thousands of patients have been safely monitored. No adverse events (AEs) related to the system have been reported during all years of monitoring.

1.3.2 Advanced Neonatal Epidermal System, Sonica

Sonica, a small technology group based out of Northwestern University in Evanston, Illinois, United States, has developed a system of neonatal non-invasive adhesive sensors that allow wireless, advanced monitoring for neonatal intensive care. This advanced neonatal epidermal (ANNE) system consists of one sensor which contains Bluetooth technology with a built-in battery and a second sensor that is battery-free and ultra-thin. The sensors can be attached directly on the patient's body and are capable of continuously measuring and recording HR, RR, oxygen saturation (SpO2), and skin temperature. Information from the sensors are wirelessly transmitted to a monitor or mobile device and the monitoring is supported by customized software.

The Sonica ANNE system utilizes existing off-the-shelf, hypo-allergenic adhesives manufactured by Cardinal Health.⁵ This hydrogel material has low allergenicity and low peel force. It is used worldwide as an adhesive for neonatal applications. The device itself is current-isolated with no energy or current being delivered from the device to the neonate. It has been validated in more than 50 neonates cared for in the neonatal care unit without a single AE.

1.4 Reference Devices

The Rad-97[™] device, developed by Masimo, provides continuous physiological monitoring in a compact, portable, device. The device is capable of monitoring HR, RR, SpO2, and capnography in adult, pediatric, and neonatal patients. Patient information can be transmitted from the device via Ethernet or USB port to wired infrastructures such as traditional nurse call systems or wirelessly via Wi-Fi or Bluetooth technology. This device is similar to devices such

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as blood pressure monitors or cardiopulmonary monitors (monitors HR and RR) that wirelessly communicate, via Wi-Fi or Bluetooth technology, information regarding a newborn's vital signs to a hospital's patient monitoring system within a newborn care unit and NICU.

Temperature will be measured using the Tempo Easy Bleu by Spengler. This non-contact infrared thermometer predicts core body temperature from the temporal artery temperature at a distance of 3-5 cm from the forehead as well as surface or skin temperature.

2 STUDY HYPOTHESES, OBJECTIVES AND ENDPOINTS

2.1 Study Hypotheses

- The investigational device is non-inferior to the reference device(s) for each relevant measurement parameter of interest among neonates.
- The investigational device is feasible, usable and acceptable for use in neonates in a LRS.

2.2 Study Objectives

2.2.1 Primary Objectives

- To assess agreement between repeat observations by the investigational device and the reference device(s) for each relevant measurement parameter of interest based on a priori-determined non-inferiority margins among neonates.
- To compare clinical event detection performance between the investigational device and the reference device(s).
- To determine whether the investigational device is feasible, usable and acceptable among HCPs, hospital administrators and caregivers of neonates.

2.2.2 Secondary Objectives

- To assess diagnostic performance for each relevant measurement parameter of interest based on sensitivity, specificity, positive predictive value, and negative predictive value compared to the reference device(s).
- To determine the downtime performance of the investigational device.
- To determine the alarm rate (events/hour) and the number of true/false alarms of the investigational device compared to the reference device(s).
- To determine the delay time between the investigational device and the reference device(s) in true events.
- To determine the number of adverse device effects (ADEs) and serious adverse events (SAEs) resulting in skin damage during use of the investigational device.

2.3 Study Endpoints

2.3.1 Primary Endpoints

- Agreement of the relevant measurement parameters of interest between the investigational device and the reference device(s) at each observation.
- Agreement of clinical event detection between the investigational device and the reference device(s) at each observation.
- Feasibility, usability and acceptability of the investigational device among HCPs and hospital administrators.
- Acceptability of the investigational device among caregivers.

2.3.2 Secondary Endpoints

- Diagnostic performance of the investigational device to appropriately identify the following critical events:
 - a. Low HR
 - b. High HR
 - c. Low RR
 - d. High RR
 - e. Oxygen desaturation (SpO2)
 - f. Apnea
 - g. Low temperature
 - h. High temperature
- Downtime duration of the investigational device.
- Alarm rate (events/hour and ratio of false positives to missed critical events of the investigational device's alarms compared to the reference device(s)' alarms.
- Response time of the investigational device's alarms compared to the reference device(s)' alarms for critical events.
- Proportion of neonates with ADEs and SAEs resulting in skin damage.

3 METHODOLOGY

3.1 Study Design

This is a diagnostic accuracy evaluation and clinical feasibility study of investigational devices (EarlySense and ANNE systems) in a neonatal high dependency unit (nHDU) in a private teaching hospital and a government maternity hospital in Nairobi, Kenya. Neonates who are admitted for routine observation and care will be enrolled.

The project consists of two phases: 1. a verification and accuracy evaluation phase and 2. a clinical feasibility phase.

Phase I: The first phase of the study will be conducted at Aga Khan University – Nairobi (AKU-N) nHDU. Prior to initiating the accuracy evaluation of each investigational device, verification of the reference devices (Masimo Rad-97[™] and Tempo Easy Bleu) will be undertaken to ensure they are robustly functional and to confirm their within subject repeatability. Conducting

this verification will be critical to informing subsequent activities and Go/No Go criteria in the study. Neonates enrolled during reference device verification will continue to receive local standard of care while being observed intermittently for vital signs collection for a minimum of 1 hour using the Masimo Rad-97[™] and intermittent measurements with the Tempo Easy Bleu. Observations will include video recordings of the neonate and the Masimo reference device monitor for later review to facilitate manual count observations in order to determine the repeatability of the reference device. Reliability information gathered from the reference devices will be utilized to determine the specific Go/No Go criteria for each investigational device. Further evaluation of each investigational device will only proceed should these criteria be met.

Enrollment in the accuracy evaluation of the investigational devices, EarlySense system and ANNE system, will be initiated to formally assess their accuracy compared to the verified reference device(s). Enrolled neonates will continue to receive local standard of care while having vital signs collected from the reference device(s) as well as one or both of the investigational devices. Placement of the reference and investigational devices will be done in a manner that will not interfere with the neonate's clinical care. Observations will be collected for a minimum of 1 hour and will consist of videotaping and/or taking photos of the neonate during the observation period after obtaining informed consent from the caregiver. Information collected during the accuracy evaluation along with the *a priori*–determined Go/No Go criteria established during verification of the reference devices will define which, if any, of the investigational devices will move forward with additional rounds of testing or into the clinical feasibility phase at Pumwani Maternity Hospital (PMH).

Phase II: Enrollment in the clinical feasibility phase will occur in PMH's newborn unit. Similar to the verification and accuracy evaluation phase at AKU-N, enrolled neonates will receive local standard of care while being monitored with the reference device(s) as well as one or both of the investigational devices. Observations will be collected for a minimum of 1 hour and involve measurement of vital signs via the reference and investigational devices and monitoring for any critical event (i.e., low or high heart rate, respiratory rate or temperature or oxygen desaturation and apnea). Participation in the study will not interfere with or unnecessarily delay the clinical care of the neonates. However, the investigational devices will not be used to inform clinical care. During the clinical feasibility phase, ETNA site study staff and PMH HCPs will be blinded to the data collected from the investigational devices to prevent interference with clinical care.

Qualitative data collection will also be done to assess the feasibility, usability, and acceptability of the investigational devices) for monitoring of neonates in an African-setting. In-depth interviews (IDIs) and direct observations will take place at each site to assess feasibility, usability, and acceptability. Each IDI will be audio recorded. All ETNA study HCPs and hospital administrators may be involved in this portion of the study. All caregivers with a neonate enrolled in the study may also be asked if they would like to participate in the qualitative portion of the study.

3.2 Study Sites

3.2.1 Aga Khan University – Nairobi

Aga Khan University – Nairobi (AKU-N) is a private, not-for-profit university teaching hospital that receives referrals from both within and outside Kenya in the Eastern and Central African

region. AKU-N is Joint Commission International accredited and moving to Academic Medical Center standards in the next review. AKU-N sees approximately 650,000 patients in 45 outpatient clinics, 120,000 patients in the emergency department, performs approximately 12,000 surgeries, and delivers 4500 babies per year. The AKU- N NICU is the first in the East African region and has a 4-bed capacity but can be expanded to 8 beds when necessary. Neonates weighing <1000 grams are cared for in the NICU while sick neonates weighing >1000 grams are placed in the nHDU. Neonates in the nHDU are not critically ill but still require close monitoring, typically with continuous physiological monitoring. The AKU-N nHDU admits 5-10 neonates per week and the median length of stay is about 7 days. The nHDU has an 8 bed capacity and the nurse to neonate ratio is approximately 1:3. AKU-N also houses the busiest private hospital maternity unit in Nairobi where neonates may also be observed and monitored in the post-natal ward. Staffing at AKU-N includes 2 full-time faculty neonatologists, 3 private neonatologists, 2 full-time pediatric surgeons, a critical care pediatrician, a pediatric pulmonologist supported by a senior resident and 4 junior residents. NICU-trained and non-trained nurses work in mixed shifts for expertise support. Primary reasons for admissions to the nHDU include: prematurity; asphyxia; respiratory distress syndrome: transient tachypnea; sepsis; jaundice; hypoglycemia; complex congenital heart disease; meconium aspiration syndrome; low birth weight; congenital anomalies; congenital diaphragmatic hernia; and persistent pulmonary hypertension.

3.2.2 Pumwani Maternity Hospital

Founded in 1926 and currently under management of the Nairobi County government, Pumwani Maternity Hospital (PMH) is the largest referral maternity hospital in sub-Saharan Africa (reportedly the third busiest maternity hospital on the continent) and serves a population of 5 million in Nairobi and the surrounding area. PMH has 354 obstetric beds, 144 baby cots, and 50-100 daily deliveries (10-15 Caesarean sections). PMH is a training center for kangaroo mother care which is widely practiced at the facility. Neonates are managed in shared incubators with oxygen in the same room as their mothers, and mothers are also enlisted to perform nursing duties. PMH has no NICU or nHDU, no neonatal facilities for cardiorespiratory support, and no functional microbiology laboratory. There are on average 75 babies in the newborn unit daily with an average length of stay of 5-7 days. Sick neonates include those with hypoxia and suspected sepsis. PMH is run by a medical superintendent who is also a pediatrician and is staffed by 23 nurses, with 3 nurses working per shift. The nurse per neonate ratio is 1:25 and 6-7 out of the 25 neonates are sick.

3.3 Study Population

3.3.1 Study Population Overview

Enrolled neonates at each site will be representative of the ethnic demographics in Nairobi, Kenya. Both female and male neonates will be enrolled for a total participant population of up to 500 neonates.

3.3.2 Participant Eligibility

The study will enroll neonates admitted for routine observation and care at AKU-N or PMH.

Inclusion Criteria

- 1. Male or female neonate, corrected age of \leq 28 days.
- 2. Willingness and ability of neonate's caregiver to provide informed consent and to be available for follow-up for the planned duration of the study.

Exclusion Criteria

- 1. Receiving mechanical ventilation or continuous positive airway pressure (CPAP).
- 2. Skin abnormalities in the nasopharynx and/or oropharynx.
- 3. Contraindication to application of skin sensors.
- 4. Known arrhythmia.
- 5. Presence of a congenital abnormality requiring major surgical intervention.
- 6. Any medical or psychosocial condition or circumstance that, in the opinion of the investigators, would interfere with the conduct of the study or for which study participation might jeopardize the neonate's health.

For the feasibility, usability and acceptability assessment, ETNA study HCPs and hospital administrators will be enrolled if they are 18 years or older, involved in or aware of the ETNA study, and have provided written informed consent. Caregivers may be enrolled if they are 18 years or older, have a neonate enrolled in the study, and are willing to participate in a 30-minute IDI as well as direct observation while their neonate is on or attached to the investigational devices.

3.3.3 Sample Size

A total of up to 500 neonates will be enrolled. For the verification of the reference devices, up to 20 neonates will be enrolled in the AKU-N nHDU or post-natal ward. Once this initial testing and data collection of the reference devices is complete, up to 120 neonates per investigational device will be enrolled in the AKU-N nHDU or post-natal ward for a total of 240 neonates. Enrollment will then move to PMH for the clinical feasibility phase, and up to 120 neonates per investigational device will be enrolled for a total of 240 neonates.

For the feasibility, usability, and acceptability assessment, all ETNA study HCPs and relevant hospital administrators will be asked to participate in the data collection procedures. Caregivers who consent to participate in the acceptability assessment may participate in an IDI as well as direct observation while their neonate is being monitored by the reference and/or investigational devices. Up to 30 caregivers at each site will be enrolled.

3.4 Study Period

Following enrollment, each neonate will be observed for a minimum of 1 hour and potentially for the entire duration of their stay in the hospital. A neonate may be enrolled to the study more than once as long as they meet the eligibility criteria and the caregiver(s) is willing to have their neonate participate. Projected duration of enrollment is anticipated to be about 12 months for this study.

4 STUDY PROCEDURES

Note that at study initiation, a pilot study will be conducted in up to 10 study participants. For these study participants, all study procedures as outlined below will be followed. The purpose of this pilot study is to evaluate and optimize study procedures and ensure study feasibility in a

situation that mirrors the clinical trial. All data collected from study participants enrolled in the pilot study will be maintained in a separate pilot study database and will not be analyzed with the study data from the main trial. The target enrollment of 500 participants for the main trial does not include the study participants enrolled in the study pilot.

Refer to Appendix I for Study Flow Diagram and Appendix II for Study Procedures and Visits Table.

4.1 Recruitment

Recruitment for this study will be performed by ETNA study staff. Neonates ≤28 days corrected age admitted to the AKU-N nHDU or post-natal ward and the PMH newborn unit will be assessed by ETNA study staff for potential screening for the study. A brief introduction to the study will be provided to the caregiver(s) to see if the caregiver is interested in learning more about the study and in potentially having their neonate assessed for eligibility.

All hospital staff involved in ETNA study recruitment procedures will be trained in relevant study-specific procedures and certified in good clinical practice (GCP). Each recruitment and referral interaction will be documented for study records.

4.2 Screening

Screening procedures are conducted by ETNA study staff to determine eligibility for enrollment in the study. All inclusion/exclusion criteria must be assessed at time of admission. The following procedures will be performed by ETNA study staff for screening:

- Provide information on the study and answer any questions.
- Assess all eligibility criteria, including if the baby is on mechanical ventilation or CPAP, skin abnormalities of the nasopharynx and/or oropharynx, any contraindications for skin sensors, arrhythmia, and presence of congenital abnormality.
- Collect de-identified demographic information.

For those neonates who are not eligible, ETNA study staff will inform the caregiver(s) that their neonate will not be able to participate in the study and will continue to receive hospital standard care. There will be no preferential treatment of study participants. All screening procedures will be documented in the appropriate study forms, including logs and case report forms. Clinical assessments and findings will also be documented in the neonate's medical record, as appropriate. No identifying information will be retained for any neonate who does not enroll in the study.

4.3 Informed Consent Process

For the purposes of this protocol, "caregiver" refers to the neonate's parent(s). Informed consent will be obtained from each neonate's caregiver to ensure that the caregiver is informed of and fully understands what will and may happen to their neonate while participating in this research study. ETNA study staff will administer a comprehension checklist to potential participants' caregivers prior to obtaining written informed consent to ensure that caregivers fully comprehend the nature of the study. The informed consent process continues throughout the study. Key study concepts will be reviewed periodically with the caregivers. Additionally, if any new information is learned that may affect the caregiver's decision to stay in the study, this information will be shared with the caregivers in writing. All consent materials will be approved

by the appropriate Institutional Review Boards (IRBs) prior to use. Approval will also be sought from the Kenyan Pharmacy and Poisons Board and the Kenyan National Council for Science and Technology Bioethics Committee as required by Kenyan legislation. These will be presented to county and hospital leadership for administrative approval as well.

Written informed consent will be collected from all HCPs and hospital administrators participating in the qualitative portion of the study. HCPs and hospital administrators may decline to participate without any negative effects on their employment. Caregivers may decline to participate in the qualitative portion of the study and still have their neonate participate in the primary portion of the study.

Refer to detailed description of informed consent procedures and ethics committee approval in Section 11 (Ethical Considerations and Consent).

4.4 Enrollment

After screening is complete, ETNA study staff will perform the enrollment visit procedures for those neonates who are eligible and whose caregiver(s) is willing to participate. The following procedures will be performed at enrollment:

- Obtain written informed consent for enrollment.
- Assign participant identification (ID) study number.
- Collect gestational age/corrected age, medical history, and any additional sociodemographic information not already collected during screening.
- Collect information regarding duration of pregnancy, mode of delivery, and Apgar score results.
- Collect information regarding medications.
- Place reference and/or investigational device(s) on neonate.
- Obtain baseline vital signs.

All ETNA study enrollment procedures will be documented in the appropriate study forms. Clinical assessments and findings will also be documented in the neonate's medical record, as appropriate.

For HCPs and hospital administrators who consent to participate in the qualitative portion of the study, they will undergo an IDI after they have completed at least one month of work on the study. For caregivers who consent to participate in the qualitative portion of the study, they may undergo an IDI at any time during their neonate's participation in the study, depending on when is most convenient for the caregiver. The IDI will not exceed 30 minutes and will be conducted by a trained ETNA study staff member using a questionnaire.

4.5 Observations

Observations while the investigational device(s) and reference device(s) are in use are a minimum of 1 hour. Observations will occur in the hospital while the neonate is receiving clinical care. During observations, the following procedures will be done:

• Update medical history, including clinical procedures, interventions, therapies, additional bloodwork or laboratory tests.

1	
1	
2	Indate information regarding medications
3	• Opuale information regarding medications.
4	 Collect information about environmental features and exposures during
5	hospitalization.
6	 Check placement of reference and investigational device(s). Assess and collect
7	information regarding reference and/or investigational device(s) removal.
8	repositioning or dislodgement
9	 Set up videotane recorder and/or take photographs of peopate and the device/s)
10	• Set-up videotape recorder and/or take photographs of neonate and the device(s).
11	The neonate's face will not be recorded of photographed. Please refer to the ETNA
12	Study Manual for Instructions on appropriate photography and videotape recorder
13	placement.
14	 Track and record any of the following activities during monitoring:
15	 Kangaroo mother care.
16	 Feeding.
17	 Diaper change / clothes change.
18	 Repositioning of the neonate
19	
20	 Bathing
20	 Datiling. Clinical procedures including bloodwork, line insertion, passagetric tube.
21	• Cinical procedures including biodowork, line insertion, hasogastic tube
22	placement, umbilical wound care, drug administration, UV therapy and/or
23	stimulation.
24	 Assess for safety issues and report safety events.
25	
26	4.6 Interrupted or Missed Observations
27	If at any time during enrollment a neonate's observation is interrupted or discontinued (i.e., due
28	to clinical procedures, kangaroo mother care, feeding, diaper/clothes change, repositioning of
29	the neonate or bathing etc.) FTNA study staff will attempt to place the reference device(s)
30	and/or investigational device(s) back on the peopate to resume observations. Prior to
31	attempting to place any device back on a peopate. ETNA study staff will ensure that this
32	attempting to place any device back on a neonate, ETNA study stall will ensure that this
33	activity does not interfere with any clinical care or treatment of the neonate. Study staff will
34	attempt to place the reference device (s) and/or investigational device(s) until successful for up
35	to 30 minutes, with 30 minutes period of rest between each attempt. Any attempt at placement
36	will be discontinued if requested by the caregiver or clinical staff.
37	
38	4.7 Withdrawal and Early Termination
39	Neonates and their caregivers may voluntarily withdraw from the ETNA study for any reason at
40	any time. The ETNA site investigators may also withdraw neonates from the study in order to
41	protect their safety if in the investigators' opinion, continuing participation would jeopardize the
42	neonate's health HCPs hospital administrators and caregivers may voluntarily withdraw from
43	the qualitative notion of the study for any reason at any time. Any participant withdrawal or
44	and quantative portion of the study for any reason at any time. Any participant witholdward of
45	eany termination will be documented in the appropriate study forms.
46	
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49	4.8 Study Termination
50	Study participation will conclude prior to discharging of the neonate from the unit. The ETNA
51	study staff will liaise with the hospital staff to be notified of when a participant will be
52	discharged. At the conclusion of participation, the following procedures will be conducted:
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- Update medical history, including clinical procedures, interventions, therapies, additional bloodwork or laboratory tests.
- Update information regarding medications.
- Remove reference and investigational device(s).
- Document contact in neonate's study records.

5 STUDY DEVICES

5.1 Descriptions

This study will utilize the following reference and investigational devices:

Reference devices:

- Masimo Rad-97[™] is the reference or comparator device for the following physiological measurement parameters of interest: HR, RR, SpO2, and capnography.
- Tempo Easy Bleu thermometer is the reference or comparator device that will be used to measure skin temperature.

Investigational devices:

- EarlySense system is an investigational device that will be tested in comparison to the Masimo Rad-97[™] reference devices to measure the following physiological measurement parameters of interest: HR, RR, and apnea.
- ANNE system is an investigational device that will be tested in comparison to the Masimo Rad-97[™] and the Tempo Easy Bleu thermometer reference devices to measure the following physiological measurement parameters of interest: HR, RR, SpO2, and skin temperature.

Further details describing each of the investigational devices and their components are detailed in section 1.3 "Investigational Devices" as well as the specific reference and investigational device standard operating procedures (SOP) documents.

5.2 Method for Assigning Participants

The reference and investigational devices will be assigned to enrolled neonates at time of enrollment based on availability of devices and, if possible, both investigational devices may be placed on the neonate simultaneously.

5.3 Placement of the Devices

Detailed instructions on how to appropriately place the Masimo Rad-97[™], Tempo Easy thermometer, EarlySense system, or ANNE system components, as well as troubleshooting issues with placement or device readings, are outlined in the reference and investigational device specific SOPs: the Masimo Rad-97[™] device SOP, Tempo Easy thermometer SOP, the EarlySense system SOP, and ANNE system SOP.

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5.4 Blinding of Study

During the clinical feasibility phase, hospital and site study staff will be blinded to data collected by the investigational devices. While they will have access to the monitor or display screens for the Masimo Rad-97[™] and Tempo Easy Bleu thermometer for clinical care of the enrolled neonate while in use for the study, any and all EarlySense system or ANNE system monitors or display screens, will be blank or covered fully. Data from the investigational devices will continue to be collected and recorded for analysis. The alarms and audio alerts from all devices will be disabled, however, events that may trigger an alarm will continue to be monitored and recorded.

5.5 Packaging

Details regarding packaging of the reference and investigational devices can be found in the Masimo Rad-97[™] device SOP, Tempo Easy thermometer SOP, the EarlySense system SOP, and ANNE system SOP.

5.6 Receiving, Storage, Dispensing and Return

Details regarding receipt, storage, dispensing, and return of the reference and investigational devices can be found in the Masimo Rad-97[™] device SOP, Tempo Easy thermometer SOP, the EarlySense system SOP, and ANNE system SOP.

6 DATA COLLECTION

All ETNA clinical research data, including data collected from the reference and investigational devices, will be maintained through a combination of secure electronic data management system and physical files with restricted access. Data related to study endpoints will be uploaded from the devices to electronic databases and then extracted from the electronic databases for statistical analysis. A separate secure database will be used to store potentially identifiable information. This database will link identifiable information to participant ID. All documentation (paper-based or electronic) that has both personal identifiers and the participant ID will have restricted access and will be stored in a secure manner separately from other study data. All ETNA databases will be retained for at least five years after the last participating neonate exits the study.

6.1 Case Report Forms

ETNA study data will be collected by ETNA study staff using designated source documents or case report forms (CRFs). ETNA study data will be entered directly into the CRFs during study observations. The neonate will only be identified in the CRF by a unique participant ID. Data from the CRFs will be entered into the electronic database as promptly as is feasible. ETNA study staff will maintain source documents for each neonate at the study site. Source documentation will be available for review to ensure that the collected data are consistent with the CRFs. CRFs, source documents and other supporting documents (both electronic and paper-based) will be kept in a secure location and remain separate from participant identification information (name, address, etc.) to ensure confidentiality. GCP will be followed to ensure accurate, reliable and consistent data collection.

6.2 Questionnaires

Qualitative data will be collected through IDIs and recorded on a paper questionnaire by the ETNA study staff. Similar to the CRFs, data from the questionnaires will be entered into an electronic database as promptly as is feasible. The paper copy of the questionnaire will be maintained as source document for each HCP, hospital administrator, or caregiver enrolled to the qualitative portion of the study. No identifying information will be collected on the questionnaire. Paper questionnaires will be kept in a secure location and remain separate from participant identification information (name, address, etc.) to ensure confidentiality. GCP will be followed to ensure accurate, reliable and consistent data collection

6.3 Source Documents

Source documents include but are not limited to:

- Signed informed consent forms (ICFs).
- Documentation of the comprehension checklist.
- Documentation that includes dates and times of observations.
- Clinical notes.
- Paper questionnaire.

ETNA site investigators will maintain, and store in a secure manner, all source documents throughout the study. These documents will be retained for at least five years after the last neonate exits the study.

6.4 Device Data Collection

The placement of the device sensors will be documented with photo(s) and/or video(s) for each device in each neonate. Continuous physiological data and event data will be recorded from the reference and investigational devices at least once a second. All electronic data will be collected wirelessly or via a wired connection, from the reference and investigational devices to a study laptop using custom software applications from the device developers. The laptop will be backed-up to a secure sever at AKU-N on a daily basis. Data will be identified with unique file names containing the date and participant ID. No personal identifying information will be collected by either the reference or investigational devices.

6.5 Data Management

Local ETNA data management will take place at AKU-N, with support from SCUS. Data management activities include transferring reference and investigational device data, CRF data entry and validation, data cleaning, database quality control (QC), disaster recovery plans, preparation and submission of compliance reports to the funding agency, and preparation of the final study database. De-identified reference and investigational device data will be uploaded from the secure server to a secure electronic data management system to support data cleaning and statistical analyses. All transfer of data for analysis will use end-to-end encryption with two–factor authentication. An audit trail will be maintained for any de-identified data leaving AKU-N for analysis.

6.6 Data Access

The ETNA participating study sites will maintain appropriate medical and research records for this study, in compliance with GCP, regulatory, sponsoring organization and institutional

requirements for the protection of confidentiality of neonates. De-identified data will be provided to the investigators to facilitate data cleaning and analysis. De-identified reference data and device developer specific data will be provided to each device developer to facilitate device improvement and to ensure that the device developer data is synchronized with the reference data. The site will permit authorized representatives of the sponsor and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress. User rights will be provided to ETNA study staff, PIs, and co-investigators and the investigational device developers at the level appropriate for each individual's job description.

6.7 Data Storage

The ETNA site investigators and designees will maintain, and store securely, complete, accurate and current study records throughout the study. ETNA study staff will retain all study records on site for at least five years after study closure. Study records will not be destroyed prior to receiving approval for record destruction from the sponsor. Applicable records include source documents, ICFs, and notations of all contacts with the participating neonate and caregivers.

At the completion of the study, de-identified data will be transferred to a public data repository to share with other internal and external researchers.

7 SAFETY ASSESSMENT AND MONITORING

7.1 Safety Monitoring

The study site investigators will be responsible for close safety monitoring of all neonates participating in the study, and for alerting the ETNA protocol team if unexpected concerns arise. All neonates will be carefully screened to ensure that they do not demonstrate any exclusion criteria.

7.2 Adverse Device Effect

For the purposes of this study, an ADE is defined as the following: any untoward and unintended response to a medical device; this includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device; this includes any event resulting from a user error; this includes patients and users. Where the definition indicates "device", it refers to any device used in the study. This might be the device under investigation, or any market released component or instrument of the system used to implant the device.

The ETNA protocol team anticipates ADEs and SAEs to occur among enrolled neonates at a similar rate as untoward medical events occur in comparable pediatric populations outside of a research setting. ADEs that the study team expects may occur during the research include, but are not limited to: adverse reactions to the reference and investigational device sensors (e.g., erythema or edema at the sensor site). The site investigators will be assessing all ADEs resulting in skin damage and treat or refer the participating neonate for medical care as appropriate, which may include removal of the device(s) and withdrawal of the neonate from the study if necessary. If any acute treatment or medical care is required as a result of harm caused by investigational and/or reference devices or study procedures, this care will be

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provided by the site free of charge. All neonates in the study with an ADE resulting in skin damage will be followed clinically until the ADE resolves (returns to baseline) or stabilizes.

7.3 Serious Adverse Events

A SAE will be defined as any ADE resulting in permanent skin damage..

7.4 Adverse Event Relationship to Devices

The relationship of ADEs (skin damage) to the investigational or reference device(s) will be assessed as follows:

- Definitely related: ADE and administration of the device are related in time, and a direct association can be demonstrated with the device.
- Probably related: ADE and administration of the device are reasonably related in time, and the ADE is more likely explained by the device than by other causes.
- Possibly related: ADE and administration of the device are reasonably related in time, and the ADE can be explained equally well by causes other than the device.
- Probably not related: a potential relationship between administration of the device and ADE could exist, but is unlikely, and the ADE is most likely explained by causes other than the device.
- Not related: the ADE is clearly explained by another cause unrelated to administration of the device. Reportable events must have documentation to support the determination of "not related."

The initial determination of ADE relationship to the device will be made by study staff with as needed consultation with the local site investigators. An independent medical monitor will review determinations of ADE relationship and assign the final relationship determination, including all SAEs.

7.5 Grading Severity of Events

Any ADE resulting in erythema or edema that does not resolve within 12 hours will be assessed and reported.

Skin condition at the sensor site will be assessed based on severity of erythema and edema, as well as skin breakdown.

7.6 Safety Reporting

All ADEs and SAEs must be reported by the site to the study medical officer and sponsor within 24 hours. Photographs of ADE will be taken and included in the report. Attribution with regard to relationship to the device will only be reported for all ADEs and SAEs. Any ADE described by the site staff as probably, or definitely related to the device requires immediate notification by the site study staff to the medical officer, co-PIs, and sponsor. These ADE cases will be forwarded to an independent medical monitor for review and the independent medical monitor will make the final determination of relationship to the study device. The independent medical monitor, study medical officer, co-PIs, and sponsor will convene within 24 hours by teleconference and decide whether the event necessitates a pause in further enrollment.

. Reporting requirements for the IRB will be followed as appropriate.

8 TRAINING REQUIREMENTS, MONITORING AND REPORTING

8.1 Training Requirements

All ETNA study staff will be trained in the Protection of Human Subjects and GCP prior to any interactions with study participants. Prior to study initiation, all ETNA study staff will receive training on all study procedures, including the study protocol, SOPs, data collection tools, informed consent process and reporting. Trainings will be conducted by a representative of the study sponsor or study consortium or other qualified clinician, as appropriate for the training material. ETNA study staff involved in placement and handling of the devices will be trained by qualified individuals from the sponsor or device developers.

8.2 Monitoring

The ETNA study site investigators will be responsible for close safety monitoring of all neonates participating in the study, and for alerting the ETNA protocol team if unexpected concerns arise. All neonates will be screened carefully prior to enrollment to ensure that neonates do not demonstrate any exclusion criteria. This study does not involve any direct diagnosis, treatment, or intervention, so each participating neonate will be cared for per local standard of care by hospital staff, independent of ETNA study activities.

ETNA study investigators will hold regular conference calls to monitor progress and ensure homogeneity and safety in protocol execution.

8.3 Study Discontinuation

The ETNA study may be discontinued at any time by the ETNA protocol team, funding agency, regulatory authorities, or IRBs.

9 STATISTICAL DESIGN AND ANALYSIS

9.1 Overview and General Design

The goal of the ETNA study is to determine the accuracy and clinical feasibility of two investigational non-invasive continuous physiological monitoring devices in neonates in a LRS. We will initially perform verification of the reference devices in a cohort of 20 neonates. We will determine repeatability using within subject repeated observations of the relevant parameters of interest. The reference device measurements will be compared to manual measurements, clinical monitor observations, and video-assisted observations.

We will then asses accuracy of the investigational devices by measuring the agreement between the reference device(s) and each investigational device using repeated observations in a new cohort of 20 neonates. Agreement between the reference and investigational device(s) will be determined using an *a priori*-defined non-inferiority threshold. Thresholds will be determined based on the repeated observations performed on the reference device in the verification phase, international standards and clinical expert consensus opinion. Two *a priori*-determined thresholds will be determined: one lower threshold that would allow the device developer to optimize the device for retesting, and a second higher threshold that will allow the device to move on to the clinical feasibility phase of testing. A maximum of five rounds of testing and retesting will be permitted for each investigational device. Each round of testing or

retesting will consist of using an additional cohort of 20 neonates. Should the lower threshold not be reached for at least one parameter, no further testing of the investigational device will be performed.

An investigational device will advance to the clinical feasibility phase once the agreement for the measurement parameters of interest exceed the higher non-inferiority threshold. The clinical feasibility phase will be performed in a less-controlled environment at PMH in a cohort of up to 120 neonates for each device. We will evaluate the agreement between repeated observations from the reference device(s) and the investigational device(s) as well as diagnostic performance in clinical event detection. Additional performance metrics such as alarm rates, alarm delays and uptime\downtime will be compared between the reference and investigational devices.

9.2 Analytical Methodology

Every second of data will be automatically graded according to the quality of the data for each measurement parameter of interest. The quality will be graded as *optimal, acceptable* and *unacceptable* based on predefined rules for each device and each measurement parameter of interest. The Masimo Rad-97[™] provides a signal quality index that will be used to determine data quality. Each of the investigational devices also provide a signal quality index. The quality thresholds will be determined following the verification phase. All comparisons will be performed from observations between two devices (or a single device during the verification phase). We will randomly select multiple (a least 10) observations of 120 seconds of optimal quality data in each neonate, at least five minutes apart, for each measurement parameter of interest from the full recording. For the clinical feasibility phase, accuracy comparisons will use optimal or acceptable data. We will use at least three hours of recording to a maximum of 12 hours for the performance metrics such as alarm rates, alarm delays and uptime\downtime.

The repeatability of the reference device parameter estimates initially will be assessed with the intraclass correlation coefficient (ICC). Additional training or standardization of procedures will be performed to ensure at least good repeatability (ICC >0.7). This will be followed by measuring agreement between the repeated reference observations and between the manual, clinical monitor and video-assisted methods and the reference observations using the methods described by Bland and Altman for replicated observations.⁶ The agreement will be reported as a mean bias and limits of agreement with 95% confidence intervals (CIs). Graphical representation of the data will be assessed with agreement plots, Clark error grids, and Polar plots to identify extreme outliers and significant data trends. We will extend the reliability analysis using inter-rater and intra-rater reliability with an equivalence test for agreement.⁷

In the accuracy evaluation, we will calculate the root mean square difference (RMSD) and ICC for each measurement parameter of interest to compare the multiple repeated observations between the reference and investigational devices. We will then calculate the agreement between the reference device(s) and each investigational device using the methods described by Bland and Altman for replicated observations. The agreement will be reported as a mean bias and limits of agreement with 95% CIs. Graphical representation of the data will be assessed with agreement plots, Clark error grids, and Polar plots to identify extreme outliers, impact on clinical decisions, and significant data trends. We will use an *a priori*-defined non-inferiority margin for agreement as a threshold value to allow for decisions regarding proceeding to additional testing.

In the clinical feasibility phase, agreement between the reference device(s) and each investigational device will be assessed as in the accuracy evaluation phase. Event detection rates, alarm rates, alarm delays and uptime/ downtime will be summarized with means, medians, standard deviations and intra-quartile ranges as appropriate. Summaries of sensitivity, specificity, positive predictive values and negative predictive values comparing each measurement parameter of interest in the investigational device(s) to the reference device(s) will be produced. Comparisons of binary events will be assessed using Cohen's weighted Kappa and McNemar's test. The non-inferiority of alarm rates, alarm delays and uptime/ downtime will be evaluated based on predefined inferiority margins.

Qualitative data will be collected through IDIs and/or semi-structured questionnaires and analyzed to assess feasibility, usability and acceptability of the investigational devices among HCPs and hospital administrators, and acceptability among caregivers of enrolled neonates. The qualitative data will be in narrative format and the results will be descriptive. The questionnaires will be coded and analyzed using a codebook with identified themes, including feasibility of using each investigational device, barriers and facilitators to use, and perceived value. Qualitative data analysis software will be used to organize, code, and analyze the qualitative data in an iterative process. The research team will start by identifying an initial set of codes and themes based on the categories from the IDI guides. During the coding process, attention will be paid to identifying emergent issues and themes that will be added to the codebook and included in the analysis. Responses from the IDIs will be coded and discrepancies will be discussed and resolved for the final analysis and theme identification.

9.3 Sample Size Estimation

Sample size estimates for method comparison studies typically depend on the confidence interval required around the limits of agreement. Sample sizes of 100-200 typically provide a tight confidence interval. The standard deviation of the difference between the reference and investigational devices for RR (predicted to be the widest standard deviation of the parameters of interest measured) is estimated to be three breaths per minute for optimal data, and five breaths per minute for (to be adequate data obtained in the clinical feasibility phase at PMH).

Verification sample size: 20 neonates with 10 replications per neonate will give the 95% CI of limits of agreement between the reference device(s) and the standard clinical measurements to be +/- 0.76 times the standard deviation of their differences. This would be approximately 2.3 breaths per minute based on a standard deviation of three breaths per minute.

Accuracy sample size: 20 neonates with 10 replications per neonate per device will give the 95% CI of limits of agreement between the reference device(s) and the investigational device to be +/- 0.76 times the standard deviation of their differences.

Clinical feasibility sample size: 100 neonates per device will give the 95% Cl of limits of agreement between the reference device(s) and the investigational device to be +/- 0.34 times the standard deviation of their differences. For event detection comparison (based on a hazard ratio of 0.75), 379 events will provide 80% power to detect a 25% difference in incidence rate at 5% significance level, assuming that the same numbers of neonates are tested by the reference device(s) and the investigational device. This is assuming we collect one event per hour for 3-4 hours of recordings in each of the 100 neonates.

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10 RESULT PRESENTATION

Results of this research may be presented through published manuscript(s) with detailed description of the background, methods, results, discussion and conclusions. The specific format and details of any potential manuscript will be in accordance with the requirements of the publishing journal.

10.1 Dissemination of Results

The results of this study may be published collaboratively by ETNA investigators at SCUS, in peer-reviewed journals. ETNA study findings will be presented to staff at each study site. ETNA study results may be presented at international conference(s) to disseminate the findings of the study.

11 ETHICAL CONSIDERATIONS AND CONSENT

11.1 Principles for Clinical Research

This clinical study will be conducted in compliance with the protocol, GCP, and all applicable regulatory requirements and IRB reviews. All ETNA study activities will follow the ethical principles of the Declaration of Helsinki. All ETNA study staff will be trained and certified in the protection of human subjects.

11.2 Institutional Review Boards and Independent Ethics Committees

The IRB of record for this study is AKU-N Research Ethics Committee. A copy of the protocol, proposed ICFs, other written participant information, and any proposed advertising materials will be submitted to AKU-N Research Ethics Committee for written approval. The protocol will be submitted to Western Institutional Review Board (WIRB) as well for review and approval. The ETNA investigators must submit and, where necessary, obtain approval from the IRB at their local institution for the initiation of the study and all subsequent protocol amendments and changes to the ICF. SCUS is responsible for assuring that this protocol, ICFs and any other study-related documents are approved by AKU-N Research Ethics Committee prior to implementation of the protocol. Any subsequent amendments to the protocol or other study-related documents must be approved by AKU-N Research Ethics Committee prior to implementation. The ETNA study will be conducted in full compliance with the protocol. Any deviations from or violations of the protocol will be documented and submitted to the appropriate IRB by investigators as required. The protocol will not be amended without prior written approval by the SCUS ETNA PI.

11.3 Informed Consent Documentation

In obtaining and documenting informed consent, the ETNA site investigators and their designees will comply with applicable local and domestic regulatory requirements and will adhere to GCP. English and Swahili versions of the ICF will be reviewed and approved by the appropriate IRBs before use with participant neonates' caregivers. The ICF will include the purpose of the study, a description of the procedures to be followed and the risks and benefits of participation. The informed consent process will give caregivers all of the relevant

information necessary to decide whether to participate, or to continue participation, in this study. Potential research participant neonates' caregivers will be permitted to ask questions and to exchange information freely with the ETNA study team. If the caregiver providing consent is illiterate, an independent witness will be present to verify to the caregiver that all the information read aloud is contained in the ICF. In this instance, the caregivers will thumbprint the ICF, which will be countersigned by the impartial witness.

Before a neonate begins participation in the study, it is the ETNA site investigators' responsibility to ensure that informed consent is obtained from their caregiver after adequate explanation of the aims, methods, and potential risks and benefits of the study. The ETNA study staff obtaining consent will also sign and date the ICF. A signed and dated copy of the consent form will be given to the participant neonate's caregiver and this will be documented in the participant neonate's study record.

Before a HCP, health administrator, or caregiver begins participation in the qualitative portion of the study, the ETNA site investigators will ensure informed consent is obtained after adequate explanation of the aims, methods, and potential risks and benefits of the study have been provided to the participant. The ETNA study staff obtaining consent will also sign and date the ICF. A signed and dated copy of the consent form will be given to the participant and this will be documented in the participant's study record

11.4 Risks and Benefits

11.4.1 Risks to Participants

Coercion

Caregivers may feel coerced tor compelled to enroll in the study in order for their neonate to receive care within a research setting, which may be perceived as a higher quality than the standard of care.

Medical Management

Participation in the study has the potential to compromise a neonate's inpatient care if study procedures are prioritized. ETNA study staff will guarantee that this will not be the case, and neonates may be excluded if study staff believes that including them in the study could jeopardize their medical care in any way.

Reference and Investigational Devices

Placement and attachment of the reference and investigational devices may cause the neonate minor, temporary distress. Placement of the investigational devices (e.g. physical placement or timing of placement) has the potential to delay clinical care. ETNA study staff will guarantee that this will not be the case, and neonates may be excluded if study staff believes that including them in the study could jeopardize their medical care in any way.

11.4.2 Protection against Risks

Coercion

During the informed consent process, ETNA study staff will emphasize that the study is optional and strictly voluntary, and that the neonate will receive medical care whether enrolled in the study or not.

Medical Management

In order to minimize the possibility that participation in this study will interfere with the standard medical management of neonates, ETNA study staff will be trained in integrating research procedures with clinical care. **Clinical care will always be prioritized above research procedures.**

Reference and Investigational Devices

ETNA study staff will be trained in the appropriate placement of the reference and investigational devices' sensors to minimize discomfort to the neonates as well as to avoid interference with any assessment, treatment, or intervention necessary for clinical care.

11.4.3 Benefits to Participants

There is no direct benefit to neonates enrolled in this study.

11.5 Participant Confidentiality

The ETNA site investigators must ensure that the neonate's confidentiality is maintained. Personal identifiers will not be included in any study reports. All study records will be kept confidential in keeping with IRB regulations as well as national and local laws. Video recordings and photographs will not include the neonate's face or caregiver's face. All study procedures will be conducted in such a manner as to protect participant privacy and confidentiality to the fullest extent possible.

12 POSSIBLE CONSTRAINTS

Anticipated implementation challenges to the successful outcome of the study include:

- Delays in device development and evaluation if the investigational device developers encounter engineering or equipment issues. Regular communication between the co-Pls, co-investigators and device developers along with close monitoring of study progress will help to anticipate, prepare for and mitigate potential engineering or equipment issues that would cause delays in device development and evaluation.
- Coordinating and standardizing certain procedures across the different sites, devices, and data platforms. A study manual and SOP documents will be developed to provide clear and detailed instructions on study procedures, devices, and data management activities. Standardized training will be provided.
- Ensuring quality and consistency of implementation across the different sites. Standardized training, supervision, and oversight will be provided to ensure quality and harmonized trial procedures.
- Difficulty in recruitment of neonates. This study will be conducted at high-volume neonatal wards and maternity wards to maximize enrollment. Sensitization and outreach activities will also be conducted to aid with recruitment.
- Perception of unequal care by non-ETNA caregivers. Study participant neonates will
 receive the same standard clinical care as all other neonates in the nHDU, post-natal
 ward, and neonatal unit. Sensitization sessions with both ETNA study caregivers and
 non-ETNA study caregivers will be conducted to provide information about the study
 and answer questions.

• Difficulties with application of reference and investigational devices. Study staff will be carefully trained on how to place the reference and investigational devices appropriately and in a manner that will minimize any possibly agitation of the neonate or cause discomfort for the neonate. Reference device(s) and/or investigational device(s) will be removed if requested by a caregiver or by hospital staff.

- Appropriate investigational device set-up and maintenance. Wires for the investigational devices should not be loose, to prevent tripping and falling. Study staff will be trained on proper installation procedures for the investigational devices.
- Limited research resources at AKU-N and PMH. AKU-N is receiving funding from the United States National Institutes of Health for research administration capacity building as well as research training and mentorship from the University of Washington, Seattle, WA, USA. PMH staff involved in ETNA will participate in all relevant research and study-specific training via AKU-N. Study progress will be monitored at both sites on a weekly and monthly basis to identify areas that require additional support.

PROTOCOL REFERENCES

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APPENDICES

Appendix I: Schedule of Study Procedures and Evaluations

Activity	Screening	Enrollment	Observation	Dischar
Eligibility assessment	x			
Informed consent and				
comprehension checklist	X			
Assign participant ID	Х			
Demographics	X	X		
Medical history		Х	Х	X
Maternal pregnancy history		Х		
Medications use		Х		
Placement of reference and/or		V	V	
investigational device(s)		X	X	
Collection of vital signs		Х	Х	Х
Video tape recording and/or			v	
photographs			^	
Track clinical care and non-study			v	v
activities			^	^
Safety assessment			X	
End of study questions		•		X
Removal of reference and/or				× ×
investigational device(s)				^



Appendix II: Informed Consents

Informed Consent Form for Enrollment [Newborn caregiver]

Evaluation of Technologies for Neonates in Africa (ETNA) Study Version 1.1, 18 June 2019

Protocol title: Evaluation of Technologies for Neonates in Africa (ETNA) project

Sponsor: Save the Children Federation, Inc., United States of America

LOCAL PRINCIPAL INVESTIGATORS:

Dr. William Macharia Aga Khan University, 3rd Parklands Avenue, P O Box 30270, Nairobi Contact phone: 254-20-3661017

Introduction

You are being asked for your baby to take part in this study because your baby is less than 28 days and has been admitted to this hospital. This study is sponsored by Save the Children, an organization that promotes children's rights, provides relief and helps support children worldwide. The person in charge of this study at this hospital is Dr. William Macharia.

This is a consent form that gives you information about the study and what you or your baby will have to do if you agree to be in the study. You are free to ask questions about the study at any time. If you agree to take part in this study, you will be asked to sign this consent form or make your mark/thumbprint in front of a witness. You will be given a copy of this form to keep. Another copy will stay with the study records.

Your participation is completely voluntary. You have the right to refuse to join or withdraw from the study at any time without negative consequences to you or your baby. Before you decide, you can talk to anyone you feel comfortable with about the research. If there is anything that you do not understand about the study, please ask the study staff or Dr. Macharia at any time.

Why is this Study Being Done?

In Kenya, there is a need for safe and efficient newborn care technologies that are non-invasive, low-cost, and can operate without constant operation by a healthcare provider. We would like to adapt and test devices that can repeatedly monitor a patient's vital signs (such as heart rate, breathing, and temperature) and health status so that they can be used to reliably monitor a newborn baby in the hospital. The goal of this study is to develop and test these monitoring devices, ultimately leading to improved clinical outcomes for newborn babies.

The Bill & Melinda Gates Foundation is providing funds for this study to take place. A total of up to 500 babies admitted to Aga Khan University Hospital and Pumwani Maternity Hospital will

join this study. Each baby may be in the study for a minimum of 1 hour and up to the entire time they are in the hospital.

What Do We Expect to Learn From This Study?

From this study we expect to learn how to better develop safe, efficient, and non-invasive newborn care technologies for places like Aga Khan University Hospital and Pumwani Maternity Hospital.

What Do I Have To Do If I Take Part in the Study?

If you agree for your baby to be in the study, your baby may be observed for the entire time they are in the hospital starting from the time your baby is enrolled. The study staff will not be in charge of your baby's medical care and will not give you or your baby any study treatments or medicine. The study activities involve observing your baby and asking you questions about you and your baby. No study activities will be done on your baby before they have been fully explained to you, you have let us know that you understand the enrollment process and you have signed or made a mark/thumbprint on this form. Only after you read (or have read to you), discuss, and sign or make a mark/thumbprint on this form will your baby be enrolled in this study.

Study Enrollment

Upon enrollment, study devices may be placed on your baby to collect information on your baby's vital signs and movements. The study devices do **not** provide any type of care for your baby and cause no significant risk or harm to your baby. The hospital healthcare providers, and not the study staff, will be responsible for your baby's medical care, although a study nurse may help with providing routine care whenever such need arises on request of the hospital staff. Study devices may stay on your baby for the entire time they are in the hospital but will not interfere with normal care of your baby. Photographs and/or videos of your baby may be taken **but will not include your baby's face.** We will confirm with you before taking any photographs or videos of your child. During your baby's time in the study, they will continue to receive care from the hospital healthcare providers without interruption. For example, if the hospital doctor feels that your baby requires medication or body to body contact with you (Kangaroo mother care), your baby will be able to receive this recommended care even if they are in this study.

At enrollment, you will be asked to do the following things if you decide you want your baby to be in the study:

- Sign this form or make your mark/thumbprint on it after you have read it (or have it read to you), understand the study, and had the chance to ask questions about the study.
- Tell the study staff about your family's socio-demographics (like your education and income).
- Tell the study staff how long you were pregnant with your baby.
- Tell the study staff how your baby was delivered (vaginal birth or cesarean section).
- Tell the study staff if your baby is a twin or a triplet.
- Tell the study staff about any medical problems your baby has had.
- Your baby's weight will be recorded by a study team member.

- Your baby's vital signs will be monitored with study devices and these study devices may be placed on your baby.
- Clinical activities that take place while your baby is in the study (like medication or kangaroo mother care) will be documented.

Alternative to study participation

You have the option to not participate in this study. There will be no consequences to you or your baby if you choose not to participate in this study. Should you choose not to participate, your baby will continue to receive the normal clinical standard of care from the hospital healthcare providers.

Why Would The Doctor Take My Baby Out of This Study Early?

The study doctor may need to take your baby out of the study early if:

- The study is stopped by the sponsor, funder, ethics committee or any other regulatory body.
- If your baby is placed on mechanical ventilation or any device that assists with breathing.
- If your baby is discharged from the hospital.
- Other reasons that may prevent you and/or your baby from completing the study successfully.

What Are the Risks of Being in the Study?

- Answering questions may make you feel nervous or uncomfortable. You are free to skip any questions that you do not want to answer.
- Caregivers may feel pressured to enroll in the study in order to receive care for their baby within a research setting, which may be seen as a higher quality than the standard of care.
- Participation in the study has the potential to affect a newborn baby's inpatient care, if study procedures are prioritized. Study staff will make sure that this will not be the case, and babies may not be enrolled in the study if study staff believes that including them in the study could delay or interrupt their prompt medical attention in any way.
- Placement and attachment to the study devices may cause the newborn baby minor, temporary distress or discomfort. Placement of the study devices (e.g. physical placement or timing of placement) may also delay clinical care. Study staff will make sure that this will not be the case, and babies may not be enrolled in the study if study staff believes that including them in the study could delay or interrupt their prompt medical attention in any way.

Are There Benefits To Taking Part In This Study?

Your baby will not receive any additional benefit from being in this study. This study is designed to help understand how to develop safe, efficient, and non-invasive newborn care technologies for places like Aga Khan University Hospital and Pumwani Maternity Hospital. We hope that this technology will help babies like yours in the future.

What About Confidentiality?

All possible measures will be made to keep your and your baby's personal information private. We cannot guarantee 100% confidentiality. If this study is published, your name and/or your baby's will not be used and you and/or your baby will not be personally identified. Any photographs or videos of your baby will not include your baby's face.

In order to make sure the study is being done properly, your records may be reviewed by:

- Study staff and monitors
- Ethics Committee and/or Institutional Review Board (IRB)
- Save the Children
- University of British Columbia
- The device developers (EarlySense and Sonica)

Your baby's study records will be kept at the clinic/hospital for at least five years after the study is completed or for the duration required by Kenyan law. You may see your baby's records if you want to. If you decide to leave the study, information already collected from your baby will still be used for the study.

What Are The Costs To Me?

There is no cost to you for participation in this study.

Will I Receive Any Payment?

You will not receive any payment for participation in this study.

What Happens If My Baby Is Injured?

It is unlikely that your baby will be injured as a result of being in this study. If your baby is injured due to being in this study, your baby will be given immediate treatment. Contact Dr. William Macharia at 254-20-3661017 and he will tell you where your baby can get treatment.

What Are My Baby's Rights As A Research Participant?

Having your baby take part in the study is completely up to you. It is your choice. You may choose to have your baby stop the study procedures at any time – there will be no penalty or loss of benefits to which you/your baby are otherwise entitled. You and your baby will be treated the same no matter what you decide. If you choose to not have your baby be in the study, you and your baby will not lose the benefit of services to which you/your baby are otherwise entitled. and there will be no penalty or loss of benefits to which you/your baby are otherwise to which you would normally have at this clinic and there will be no penalty or loss of benefits to which you/your baby are otherwise entitled.

We will tell you about new information from this or other studies that may affect your baby's health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know that you would like them.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by United States of America law. This website will not include information that could identify

you and/or your baby. At most, the website will include a summary of the results. You can search this website at any time.

The research study was reviewed and approved by the Western Institutional Review Board in Washington, USA; the Aga Khan University Research Ethics Committee; the Pharmacy and Poisons Board; and the National Council for Science and Technology - National Bioethics Committee. This approval does not mean that the study is safe or that the committees approved your baby's participation.

What Do I Do If I have Problems or Questions?

For questions, concerns or complaints about the study, baby's rights as a research participant, or if your baby has a research-related injury, you should contact:

Dr. William Macharia, Aga Khan University Hospital, 3rd Parklands Avenue. Tel: 254-20-3661017; email: william.macharia@aku.edu

SIGNATURE

I have read the informed consent (or had it read and explained to me), and all my questions have been answered. I have let the study staff know that I understand and I agree for my baby to take part in this study. My signature or mark/thumbprint below documents my consent.

Name of Participant (Parent/Legal Guardian to print participating baby's name)

Name of Parent/Legal Guardian (print name)

Parent/Guardian's Signature and Date

Name of Study Staff Conducting Consent Discussion (print name) Study Staff Signature and Date

Name of Witness (print name) Witness's Signature and Date (As appropriate, if Parent/Legal Guardian is illiterate)

Fomu ya maelezo na makubaliano kwa usajili (Kwa wenye kuhudumia watoto wachanga)

Utafiti wa kutathimini/kuangalia kwa undani Teknolojia za watoto wachanga barani Africa (ETA)

Toleo la 1.1, 18 June 2019

Kichwa cha Protokali: Mradi wa kutathmini/kuangalia kwa undaniTeknolojia za watoto wachanga barani Africa (ETA)

Mdhamini: Save the Children Federation Inc., United States of America MTAFITI MKUU HAPA INCHINI: Dr. William Macharia Aga Khan University, 3rd Parklands Avenue, P O Box 30270, Nairobi Contact phone: 254-20-3661017

<u>Utangulizi</u>

Tunakuomba ukubali mtoto wako ashiriki kwenye utafiti huu kwa sababu ana umri wa chini ya siku 28 na amelazwa katika hospitali hii. Utafiti huu unadhaminiwa ni shirika la Save the Children, hili ni shirika ambalo linakuza haki za watoto, hutoa misaada na pia husaidia watoto duniani kote. Msimamizi wa utafiti huu katika hospitali hi ni Daktari William Macharia.

Hii ni fomu ya maelezo na makubaliano ambayo inakupatia maelezo kuhusu utafiti wenyewe na vile wewe ama mtoto wako atatakiwa kufanya ukikubali ajiunge na utafiti huu, Uko huru kuuliza maswali kuhusu utafiti huu wakati wowote. Ukikubali kushiriki kwenye utafiti huu, tutakuomba uweke sahihi yako kwenye fomu hii ya makubaliano au alama ya dole gumba mbele ya shahidi wako. Utapewa kopi ya nakala hii uweke. Kopi ingine itabaki kama rekodi za utafiti.

Kushiriki kwako kwenye utafiti huu ni hiari yako kabisa. Uko na haki ya kukataa kushiriki ama kujitoa kutoka kwenye utafiti huu wakati wowote bila ya matokeo yoyote mabaya kwako ama kwa mtoto wako. Kabla ya kuamua kushiriki ama kutoshiriki unaweza kuzungumza na mtu yeyote ambaye uko huru naye kuhusu utafiti huu. Kama kuna kitu chochote ambacho hukielewi kuhusu utafiti huu, tafadhali muulize **mfanyi kazi kwenye utafiti huu** ama Daktari Macharia wakati wowote.

Ni kwa nini Utafiti Huu Unafanywa?

Katiki inchi ya Kenya, kunahitajika teknolojia zisizoingiliana ambazo ni salama, zenye ufanisi na zenye gharama ya chini za kutunza watoto wachanga, ambazo zinaweza kufanya kazi bila usaidizi wa mara kwa mara kutoka kwa muhudumu wa afya. Tungependa kujaribu na kutumia vifaa ambavyo vinaweza kufuatilia mara kwa mara ishara muhimu za kiafya (kama vile mpigo wa moyo, kupumua, na joto mwilini) na hali ya afya ili ziweze kutumika kufuatilia kikamilifu mtoto

mchanga hospitalini. Lengo la utafiti huu ni kuimarisha na kujaribu vifaa hivi vya kufuatilia hali ya mgonjwa, ambavyo vitaboresha matokeo ya kiafya kwa watoto wachanga.

Taasisi ya Bill na Melinda Gates inatoa ufadhili wa kifedha ili utafiti huu ufanyike. Jumla ya watoto 500 waliolazwa katika hospitali ya Chuo Kikuu cha Aga Khan na hospitali ya kujifungulia akina mama ya Pumwani watajiunga na utafiti huu. Kila mtoto atakuwa kwenye utaiti huu kwa muda wa kati ya saa moja na muda wote ambao atakuwa bado amelazwa hospitalini.

Ni kitu gani ambacho tunatarajia kujifunza kutokana na utafiti huu?

Kutokana na utafiti huu tunatarajia kujifunza jinsi ya kubuni teknolojia zisizoingiliana za kumtunza mtoto mchanga ambazo ni salama na zenye ufanisi zitakazotumika mahali kama hapa Aga Khan University hospital na hospitali ya kujifungulia akina mama a Pumwani.

Ni kitu gani ambacho nitatakiwa kufanya nikiamua kushiriki kwenye utafiti huu?

Ukikubalia mtoto wako ashiriki kwenye utafiti huu, mtoto wako ataangaliwa kwa muda wote ambao atakuwa hapa hospitalini mara tu atakaposajiliwa kwenye utafiti huu. **Wafanyikazi kwenye utafiti huu hawatajihusisha na matibabu ya mtoto wako na hawatakupatia wewe au mtoto wako matibabu yoyote ya kiutafiti au madawa. Shughuli za utafiti zinahusisha kumuangalia mtoto wako na kukuuliza maswali kuhusu wewe mwenyewe na mtoto wako. Hakuna shughuli zozote za utafiti zitakazofanyiwa mtoto wako bila wewe kuelezwa kikamilifu kuzihusu, utatuambia kama umeuelewa mchakato/taratibu ya kusajiliwa kwenye utafiti huu na umeweka sahihi yako au alama ya dole gumba kwenye fomu hii ya kukubali kushiriki utafiti. Mtoto wako atasajiliwa kwenye utafiti huu tu iwapo/kama utaisoma (ama kusomewa), kuijadili, na kuweka sahihi yako au alama ya dole gumba kwenye fomu hii.**

Kusajiliwa kwenye utafiti

Baada ya kusajiliwa, huenda vifaa vya utafiti vikawekwa kwa mtoto wako ili **kuchukua maelezo kuhusu** hali yake (kama mpigo wa moyo, kupumua na kiwango cha joto mwilini), na harakati za kuyumbisha mwili wake. **Vifaa vya utafiti havitoi huduma yoyote ya matibabu kwa mtoto wako na wala havisababishi athari au madhara yoyote kwa mtoto wako. Wahudumu wa afya wa hospitali ndio watatoa huduma za matibabu kwa mtoto wako na wala sio wafanyikazi kwenye utafiti huu, ijapokuwa muuguzi wa utafiti anaweza kusaidia kutoa huduma za kawaida kama hali itabidi wahudumu wa afya hospitalini wakimuhitaji.** Vifaa vya utafiti huenda vikabakia kwa mtoto wako kwa muda wote atakaokuwa bado amelazwa hospitalini lakini havitasumbua utoaji wa huduma za kawaida kwake. Huenda tukachukua picha ama picha za video kwa mtoto wako **lakini picha hazitchukuwa sura yake**. Tutadhibitisha nawe kabla ya kuchukua picha ama video hizi. Mtoto wako akiwa kwenye utafiti huu, **bado ataendelea kupata huduma kutoka kwa wahudumu wa afya hospitalini bila kutatizwa.** Kwa mfano, Daktari **wa hospitali** akiona mtoto wako anahitaji kupewa dawa au kama anahitaji mkumbatio wa mama yake (Mfano wa Kangaroo anavyomtunza mtoto wake), mtoto wako ataweza kupata huduma hizi hata kama yuko kwenye utafiti. Ukiamua mtoto wako ajiunge na utafiti huu, tutakuomba ufanye mambo yafuatayo wakati tunapomsajili kwenye utafiti:

- Uweke sahihi yako au alama ya kidole gumba kwenye fomu hii baada ya kuisoma (au baada ya kusomewa), kama unauelewa utafiti wenyewe, na kama umepata nafasi ya kuuliza maswali uliyokuwa nayo kuhusu utafiti huu
- Utoe maelezo kwa muhudumu wa utafiti kuhusu familia yako (Kwa mfano hali ya elimu na mapato ya kiuchumi)
- Utoe maelezo kwa muhudumu wa utafiti uja uzito wa mtoto uliye naye ulichukuwa muda gani.
- Utoe maelezo kwa muhudumu wa utafiti mtoto uliyenaye ulijifungua kwa njia gani (Ulizaa kwa njia ya kawaida ama kwa njia ya upasuaji)
- Utoe maelezo kwa muhudumu wa utafiti kama mtoto wako ni mapacha ama uliwazaa watatu kwa hiyo mimba moja.
- Utoe maelezo kwa muhudumu wa utafiti kuhusu matatizo yoyote ya kiafya ambayo mtoto wako amekuwa nayo.
- Muhudumu wa utafiti atachukua na kurekodi uzani wa mtoto wako.
- Hali ya kiafya ya mtoto wako itafuatiliziwa kutumia vifaa vya utafiti, na hivi vifaa vya utafiti huenda vikaekelewa kwa mtoto wako.
- Mambo yote (kama vile kupewa dawa au mfano wa kangaroo anavyomtunza mtoto wake) yatakayofanyiwa mtoto wako hospitalini yatanakiliwa.

Mbadala/Badala ya kushiriki kwenye utafiti

Uko na chaguo/uamuzi wa kutoshiriki kwenye utafiti huu. Hakutakuwa na matokeo yoyote mabaya kwako au kwa mtoto wako ukiamua/ukichagua kutoshiriki kwenye utafiti huu. Hata ukiamua kutoshiriki mtoto wako **bado ataendelea** kupata huduma za matibabu zenye kiwango cha kawaida. **kutoka hapa hospitali – wanaotoa huduma za matibabu.**

Kwa nini Daktari anaweza kumtoa mtoto wangu kwenye utafiti huu mapema?

Daktari huenda akamtoa mtoto wako kwenye utafiti mapema ikiwa:

- Kama utafiti utasimamishwa ni mdhamini, mfadhili, kamati inayosimamia maadili ya utafiti ama bodi yoyote inayodhibiti mambo ya utafiti.
- o Kama mtoto wako ataekelewa mitambo ama kifaa chochote cha kumsaidia kupumua
- Kama mtoto wako atatolewa hospitalini.
- Ama sababu zingine ambazo zinaweza kukuzuwia wewe/mtoto wako kumaliza utafiti kikamilifu.

Kuna Athari Gani Zinazotokana na Kushiriki Kwenye Utafiti Huu?

• Kujibu maswali kunaweza kukufanya usijisikie huru ama kuwa na wasiwasi. Uko huru kutojibu maswali yoyote ambayo hutaki kuyajibu.
- Walezi wa watoto wanaweza kushiriki kwenye utafiti huu kutokana na shinikizo la kutaka watoto wao wapate huduma za afya ndani ya utafiti, ambayo inaweza kuonekana kama huduma ya kiwango cha hali ya juu sana kuliko kiwango cha matibabu cha kadri ya kawaida.
- Kushiriki kwako kwenye utafiti huu huenda kukaathiri matibabu/uangalizi wa mtoto mchanga aliyelazwa hospitalini, kama taratibu za utafiti zitapewa kipau mbele. Wafanyikazi kwenye utafiti huu watahakikisha hali hii haitukei, na watoto wengine huenda wasisajiliwe kwenye utafiti huu kama wafanyikazi kwenye utafiti huu wataona kwamba kuwajumuisha kwenye utafiti huenda kukachelewesha au kutatiza kupata huduma za matibabu kwa njia moja au nyengine.
- Kuweka na kupachika vifaa vya utafiti kwa mtoto mchanga huenda kukasababisha dhiki ama usumbufu kwa muda kidogo. Kupachika vifaa vya utafiti kwa mtoto (Kwa mfano kupachika vifa kwa mwili ama wakati unaotumika kupachika vifaa vya utafiti kwa mwili wa mtoto) pia huenda kukachelewesha mtoto kupata matibabu. Hata hivyo wafanyi kazi kwenye utafiti huu watahakikisha hali kama hii haitokei, na watoto wengine huenda hawatasajiliwa kwenye utafiti ikiwa wafanyi kazi kwenye utafiti wataamini kwamba kujumuishwa kwao kwenye utafiti huenda kukachelewesha ama kutatiza wao kupata matibabu kwa wakati unaofaa.

Je, kuna faida zozote zinazotokana na kushiriki kwenye utafiti huu?

Mtoto wako hatapata manufaa mengine yoyote ya ziada kwa kujiunga na utafiti huu. Utafit huu unafanywa ili kuelewa jinsi ya kubuni/kuendeleza Teknolojia zenye usalama, ufanisi na ambazo haziingiliani za kuangalia afya za watoto wachanga ili kutumika mahali kama Aga Khan University Hospital na Hospitali ya kujifungulia akina mama ya Pumwani. Tunatumaini kwamba hapo siku za usoni Teknolojia hii itasaidia watoto kama huyu wako.

<u>Na je, ni vipi kuhusu usiri?</u>

Tutafanya kila tuwezalo kuhakikisha maelezo yako na ya mtoto wako ya kibinafsi yamewekwa siri. Hata hivyo hatuwezi kukuhakikishia kwamba tutaweka siri ya maelezo yote kwa asilimia kwa mia. Na kama utafiti huu utachapishwa, jina lako/la mtoto wako halitatumka wala hamtatambulishwa. Picha au video zote za mtoto wako hazitakuwa/hazitachukuwa sura yake.

Ili kuhakikisha ikiwa utafiti huu unafanyika vizuri, rekodi/kumbukumbu zako zinaweza kuangaliwa/kupitiwa ni:

- Wafanyikazi kwenye utafiti huu na wafuatiliaji wa utafiti huu.
- Kamati inayosimamia maadili mema ya utafiti ama Institutional Review Board (IRB)
- Taasisi ya Save the Children
- o Chuo kikuu cha British Columbia
- Wenye kutengeneza vifaa (EarlySense and Sonica)

Reckodi zote za utafiti za mtoto wako zitawekwa kwenye kliniki/Hospitali kwa muda usiopungua miaka mitano baada ya kumalizika kwa utafiti ama kwa muda unaohitajika kisheria hapa inchini.

ETNA Protocol version 1.1, 18 June 2019

Pia unaweza kuona rekodi za mtoto wako ukizihitaji. Na ukiamua kujitoa kwenye uafiti, maelezo yaliyopatikana kutoka kwa mtoto wako bado yatatumika kwenye utafiti huu.

Je nitatozwa ada/garama ya kiasi gani kwa kushiriki kwenye utafiti huu?

Hautalipa ada au garama zozote kwa kushiriki kwenye utafiti huu.

Je, nitapata malipo yoyote kwa kushiriki kwenye utafiti huu?

Hautapata malipo yoyote kwa kushiriki kwenye utafiti huu.

Ni nini kitatokea kama mtoto wangu atajeruhiwa?

Hakuna uwezekano wa mtoto wako kujeruhiwa kutokana na kujiunga na utafiti huu. Na kama mtoto wako atajeruhiwa kutokana na kujiunga na utafiti huu, mtoto wako atapewa matibabu haraka sana.

Unaweza kuwasiliana na Daktari William Macharia kupitia kupitia nambari ya simu 254-20-3661017 na atakuambia ni wapi mtoto wako ataenda kupata matibabu.

Je, haki za mtoto wangu kama mshiriki kwenye utafiti huu ni zipi?

Uamuzi wa iwapo mtoto wako atashiriki kwenye utafiti huu ni wako kabisa. Ni chaguo lako. Unaweza kuamua mtoto wako akome/awache kufanyiwa taratibu za utafiti wakati wowote – hautalipizwa faini yoyote ama kukosa manufaa/faida ambazo wewe na mtoto wako ni haki yenu. Wewe na mtoto wako mutahudumiwa kiusawa bila kujali uamuzi wako uliochukua. Ukiamua mtoto wako asijiunge na utafiti huu, wewe na mtoto wako hamtakosa faida zozote za huduma ambazo kwa kawaida huwa munapata katika kliniki hii na hautatozwa faini yoyote ama kukosa manufaa/faida zozote ambazo ni haki yenu wewe na mtoto wako.

Tutakupatia maelezo mapya kuhusu utafiti huu ama tafiti zingine kama hizi ambayo huenda yakaathiri afya ya mtoto wako, maslahi yake ama kukubali kwako kuendelea kushiriki kwenye utafiti huu. Kama unataka majibu ya utafiti huu, mjulishe mfanyi kazi katika utafiti huu kwamba utayahitaji.

Maelezo ya utafiti huu yanapatikana kwenye mtandao ufuatao <u>http://www.ClinicalTrials.gov</u>, kama inavyohitajika kisheria inchini Marekani. Mtandao huu hautakuwa na maelezo yanayokutambulisha wewe na mtoto wako. Zaidi sana, mtandao huu utajumuisha matokeo ya utafiti kwa ufupi/mukhtasari. Unaweza kuutafuta mtandao huu wakati wowote.

Utafiti huu uliangaliwa na kupitishwa ni bodi ya Western Institution Review Board iliyoko mjini Washington, Marekani; Kamati ya kuangalia maadili meme ya utafiti ya Chuo Kikuuu cha Aga Khan; Bodi ya kuangalia ubora na usalama wa Madawa na Sumu; Bodi ya Kitaifa ya Sayansi na Teknolojia – Kamati ya Kitaifa ya kuangalia Maadili ya Kibayolojia. Hata hivyo kupitishwa kwa utafiti huu haimaanishi kwamba utafiti uko salama au haimaanishi kwamba Kamati hizi zilipitisha mtoto wako ajiunge na utafiti huu.

Je, nitafanya nini kama nina matatizo au maswali?

Kama uko na maswali, shaka au malalamiko kuhusu utafiti huu, haki za mtoto kama mshiriki kwenye utafiti, au kama mtoto wako ana jeraha lililotokana na utafiti, unatakiwa kuwasiliana na:

 Daktari William Macharia, Hospitali ya Chuo Kikuu cha Aga Khan , 3rd Parklands Avenue. Tel. 254-(0)203661017. Barua Pepe: <u>william.macharia@aku.edu</u>

<u>SAHIHI</u>

Nimesoma (au nimesomewa na nikapewa maelezo) fomu ya maelezo na makubaliano ya kushiriki kwenye utafiti na maswali yangu yote yamejibiwa. Nimemjulisha mfanyi kazi wa utafiti huu kwamba nimeelewa na ninakubali mtoto wangu ashiriki kwenye utafiti huu. Sahihi yangu au alama yangu ya dole gumba hapo chini yathibitisha kukubali kushiriki kwangu kwa hiari.

Jina la Mshiriki (Mzazi/Mlezi anayetambulika kisheria aandike jina la mtoto atakayeshiriki kwenye utafiti)

Jina la Mzazi/Mlezi anayetambulika Kisheria (Andika Jina) Sahihi ya Mzazi/Mlezi na tarehe

Jina la mfanyi kazi kwenye utafiti Anayepeana maelezo/maxungumzo (Andika Jina) Sahihi ya mfanyi kazi kwenye utafiti na tarehe

Jina la shahidi (Andika Jina) (Kama inavyotakikana, ikiwa mzazi/mlezi Anayetambulika kisheria hajui kusoma) Sahihi ya Shahidi na Tarehe

Informed Consent Form for Enrollment

Evaluation of Technologies for Neonates in Africa (ETNA) Study <u>Healthcare Provider/Administrator Social Sciences Sub-Study</u> Version 1.0, 14 December 2018

Protocol title: Evaluation of Technologies for Neonates in Africa (ETNA) project

Sponsor: Save the Children Federation, Inc., United States

LOCAL PRINCIPAL INVESTIGATOR AND STUDY CONTACT:

Dr. William Macharia Aga Khan University, 3rd Parklands Avenue, P O Box 30270, Nairobi Contact phone: 254-20-3661017

Part 1: Information Sheet

Introduction

You are being asked to take part in this study because you are a healthcare provider or administrator involved in the Evaluation of Technologies for Neonates in Africa (ETNA) study. The person in charge of this study at this site is Dr. William Macharia. The enrollment process includes a set of questions about the use of continuous physiologic monitoring devices used to monitor the vital signs of neonates.

This is a consent form. It gives you information about the study questions and what you have to do to be in the study. You are free to ask questions about the study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will be given a copy of this form to keep. Another copy will stay with the study records.

Your participation is voluntary and you may refuse to join or withdraw your consent at any time without any penalty. Before you decide, you can talk to anyone you feel comfortable with about the research. If there is anything that you do not understand, please ask at any time.

Why is this Study Being Done?

The goal of the ETNA study is to optimize and test two continuous physiologic monitoring devices, the EarlySense system and the ANNE system, against reference standard devices. In Kenya, there is a great need for safe and efficient newborn care technologies that are non-invasive, low-cost, and can operate without the constant oversight of a healthcare provider. While this project aims to adapt and test devices that can reliably monitor a newborn's vital signs (such as heart rate, breathing, and temperature) and health status continuously, it is also important for us to understand what healthcare providers and administrators think about the use of these continuous monitoring devices in a hospital setting. In the ETNA sub-study, we aim to learn more

about healthcare providers' and administrators' experience with and perceptions of these continuous physiologic monitoring devices.

The Bill & Melinda Gates Foundation is providing funds for this study to take place. All healthcare providers and administrators involved in the use of continuous physiologic monitoring devices during the ETNA study may be asked to take part in this study. This study is one visit only.

What Do We Expect to Learn From This Study?

- Do healthcare providers and administrators think that the use of the EarlySense system and the ANNE system is feasible in a hospital or clinical setting (i.e., could these devices be easily used to assist with care of neonates in the hospital)?
- What do healthcare providers and administrators like and dislike about these continuous physiologic monitoring devices?
- How easy is it for healthcare providers to learn how to use these continuous physiologic monitoring devices?
- What problems do healthcare providers encounter when using these continuous physiologic monitoring devices?

What Do I Have To Do If I Take Part in the Study?

If you agree to take part in the study, you will participate in one study visit. This study visit will take about 30 minutes. After signing this consent form, you will be asked questions about your experience with and perception of each of the continuous physiologic monitoring devices. An audio recording may be made of this interview. No study activities will begin before they have been fully explained to you, you have let us know that you understand the study and you have signed this form.

Alternative to study participation

You have the option to not participate in this study. There will be no negative consequences to you or your employment if you choose not to participate in this study.

What Are the Risks of Being in the Study?

Answering questions may make you feel nervous or uncomfortable. You are free to skip any questions that you do not wish to answer.

Are There Benefits To Taking Part In This Study?

There are no direct benefits to you for taking part in this study. However, the study will help healthcare researchers to learn more about continuous physiologic monitoring devices and how they might be improved for use in neonates in hospital settings. This may benefit the clinical outcomes of babies in the future.

ETNA Protocol version 1.1, 18 June 2019

What About Confidentiality?

Efforts will be made to keep your personal information private. If this study is published, your name will not be used and you will not be personally identified.

In order to make sure the study is being done properly, your records may be reviewed by:

- Study staff and monitors
- Ethics Committee and/ or Institutional Review Board (IRB)
- Save the Children, US

Your study records will be kept at the clinic/hospital for at least five years after the study is completed.

What Are The Costs To Me?

There is no cost to you for participating in this study.

What Are My Rights as a Research Participant?

Taking part in research is completely up to you. It's your choice. You may choose to stop at any time. If you choose not to be in the study, there will be no penalty to you or to your employment.

We will tell you about new information from this or other similar studies that may affect your willingness to stay in this study. If you want the results of the study, let the study staff know that you would like them.

The research study was reviewed and approved by the Western Institutional Review Board in Washington, USA; the Aga Khan University Research Ethics Committee; the Pharmacy and Poisons Board; the National Council for Science and Technology - National Bioethics Committee. This approval does not mean that the study is safe or that the committees approved your participation.

What Do I Do If I have Problems or Questions?

For questions, concerns or complaints about the study, you should contact Dr. William Macharia at 7th Floor, East Tower Block, Aga Khan University (contact phone: 254-20-3661017). We do not anticipate that you will be injured due to participation in this study.

For questions, concerns or complaints about the study or questions about your rights as a research participant, contact the Aga Khan University Research Ethics Committee.

Part 2: Certificate of Consent for Study Participation

SIGNATURE

I have read the informed consent and all of my questions have been answered. I have let the study staff know that I understand and I agree to take part in this study. My signature below documents my consent.

Participant Name (print name)	Participant Signature	Ι
Study Staff Name (print name)	Study Staff Signature	I
ETNA Protocol version 1.1, 18 Jun	48 48	

BMJ Open

Evaluation of noninvasive continuous physiological monitoring devices for neonates in Nairobi, Kenya: A research protocol

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Manuscript ID	bmjopen-2019-035184.R1
Article Type:	Protocol
Date Submitted by the Author:	13-Dec-2019
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		BMJ Open
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2 3 4	1	Title: Evaluation of noninvasive continuous physiological monitoring devices for neonates in
5 6 7	2	Nairobi, Kenya: A research protocol
8 9	3	
10 11 12	4	
13 14 15	5	Authors: Amy Sarah Ginsburg, ¹ * Evangelyn Nkwopara, ² William Macharia, ³ Roseline
16 17	6	Ochieng, ³ Mary Waiyego, ⁴ Guohai Zhou, ⁵ Roman Karasik, ⁶ Shuai Xu, ^{7,8} and J. Mark
18 19 20	7	Ansermino ⁹
21 22 23	8	
24 25 26	9	
27 28 29 30	10	¹ University of Washington, Seattle, Washington, USA
31 32 33	11	² Children's Healthcare of Atlanta, Atlanta, Georgia, USA
34 35 36	12	³ Aga Khan University, Nairobi, Kenya
37 38 39 40	13	⁴ Pumwani Maternity Hospital, Nairobi, Kenya
41 42 43	14	⁵ Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA
44 45 46	15	⁶ EarlySense Ltd., Ramat-Gan, Israel
47 48 49 50	16	⁷ Sibel Inc., Evanston, Illinois, USA
50 51 52 53	17	⁸ Northwestern University, Evanston, Illinois, USA
54 55 56	18	⁹ The University of British Columbia, Vancouver, Canada
57 58 59 60	19	

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2 3 4	20	* Corresponding aut	thor:
5 6 7 8	21	Mailing address:	University of Washington Clinical Trial Center
9 10 11	22		Building 29, Suite 250, 6200 NE 74 th Street
12 13 14 15	23		Seattle, WA, 98115, USA
16 17 18	24	Phone:	(206)616-8014
20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47			
48 49 50 51 52 53 54 55 56 57 58 59 60			2

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2 3	26	ABSTRACT
4	20	
5 6 7	27	
8 9	28	Introduction: Continuous physiological monitoring devices are often not available for
10 11 12	29	monitoring high-risk neonates in low-resource settings. Easy-to-use, noninvasive,
13 14	30	multiparameter, continuous physiological monitoring devices could be instrumental in
15 16 17	31	providing appropriate care and improving outcomes for high-risk neonates in these low-
18 19	32	resource settings.
20 21		
22	33	Methods and Analysis: The purpose of this prospective, observational, facility-based
23 24 25	34	evaluation is to provide evidence to establish whether two existing noninvasive,
26 27	35	multiparameter, continuous physiological monitoring devices developed by device
28 29 30	36	developers, EarlySense and Sibel, can accurately and reliably measure vital signs in neonates
31 32	37	(when compared to verified reference devices). We will also assess the feasibility, usability
33 34 35	38	and acceptability of these devices for use in neonates in low-resource settings in Africa. Up
36 37	39	to 500 neonates are enrolled in two phases: 1) a verification and accuracy evaluation phase at
38 39 40	40	Aga Khan University - Nairobi; and 2) a clinical feasibility phase at Pumwani Maternity Hospital in
41 42	41	Nairobi, Kenya. Both quantitative and qualitative data are collected and analyzed. Agreement
43 44 45	42	between the investigational and reference devices is determined using <i>a priori</i> -defined
46 47	43	accuracy thresholds.
48 49 50	44	Ethics and Dissemination: This trial was approved by the Aga Khan University Nairobi
51 52	45	Research Ethics Committee and the Western Institutional Review Board. We plan to
53 54 55	46	disseminate research results in peer-reviewed journals and international conferences.
56 57 58	47	ClinicalTrials.gov NCT03920761
59 60	48	

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2 3	40	Konwords: poppatos, continuous physiological monitoring devices
4	49	Reywords. Heonates, continuous physiological monitoring devices
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51	STRENGTHS AND LIMITATIONS OF THIS STUDY

53		feasibility phase, and evaluation of two novel, investigational, noninvasive, multiparameter,
54		continuous physiological monitoring devices.
55	•	A verification of the reference devices is undertaken prior to initiating the accuracy
56		evaluation of the investigational devices to ensure the reference devices are robustly
57		functional and to confirm their within subject repeatability and accuracy compare to
58		standard clinical measurements for the relevant parameters of interest.
59	•	Reliability information gathered from the reference devices is utilized to determine
60		specific <i>a priori</i> Go/No Go criteria for each parameter and each investigational device.
61	•	As with all measurements, there is uncertainty inherent in the measurements from the
62		reference devices.
63	•	Inability to control for the characteristics and conditions of the participating neonates
64		and to standardize the environment and context are both strengths and limitations to
65		interpreting the results.
66		

• This research consists of two phases, a verification and accuracy evaluation phase and a clinical

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5 4 5	67	INTRODUCTION
6 7	68	In 2017 globally, 47% of all deaths in children under 5 years of age occurred within the first
8 9 10	69	28 days of life, which translates to a neonatal mortality rate of 18 deaths per 1000 live births
11 12	70	or 2.5 million newborn deaths. ¹ Sub-Saharan Africa bears the greatest burden of neonatal
13 14 15	71	mortality with an estimated 1 million newborn deaths in 2017. Further efforts, especially in
16 17	72	African countries, are needed to push progress towards achieving the Sustainable
18 19 20	73	Development Goal (SDG) target of reducing global neonatal mortality to 12 deaths per 1000
20 21 22	74	live births by 2030. ² Without accelerated improvements, it is projected that 1.8 million
23 24 25	75	neonates will die in 2030. ³ Innovations in neonatal care, particularly technologies that allow
25 26 27	76	for early detection and intervention for major morbidities, hold great promise in helping to
28 29	77	reduce current and projected neonatal mortality rates.
30 31 32 33	78	Multiparameter continuous physiological monitoring devices could be instrumental in
34 35	79	identifying neonates at risk. We can then direct care provided for a neonate through
36 37	80	automatic interpretations of vital signs that help identify critical events and determine if
38 39 40	81	treatment is sufficient or insufficient, ultimately improving newborn outcomes. ^{4,5} These
41 42	82	devices would be most useful in low-resource settings where the need for such technologies
43 44 45	83	is greatest. While continuous physiological monitoring is standard of care in high-resource
46 47	84	settings for those who require it, the devices are expensive and require specialized training
48 49 50	85	to operate, making them unsuitable for application in low-resource settings. To address
50 51 52	86	these barriers, it is necessary to explore how these technologies can be adapted and/or
53 54	87	optimized for use in low-resource settings. Ideally, the devices should be low cost, operator-
56 57	88	independent, noninvasive and highly efficient in diagnostic performance and operator
58 59 60	89	workload. This requires development of a robust testing platform that appropriately mimics

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3 4	90	conditions common in African newborn or neonatal intensive care units that would allow
5 6 7	91	these type of technologies to be evaluated for feasibility and performance.
8 9 10	92	The Evaluation of Technologies for Neonates in Africa (ETNA) project was conceived with
11 12 13	93	the goal of advancing and supporting development, as well as evaluation, of select devices
14 15	94	for use in neonates in low-resource settings. By establishing a testing platform in an African
16 17 19	95	site, and working collaboratively with partners with expertise in device development and
19 20	96	evaluation and neonatal and child health, the project seeks to boost development and
21 22 22	97	optimization of promising newborn care devices that could be applied in low-resource
23 24 25	98	settings in Africa. We acknowledge the many challenges involved in implementing such
26 27	99	devices in low-resource settings (e.g., electricity and internet access, behavior change
28 29 30	100	communication, etc.), and the need to consider these challenges carefully prior to
31 32	101	introduction. The purpose of this initial research is to produce evidence regarding the
33 34 35	102	performance of two existing noninvasive, multiparameter, continuous physiological
36 37	103	monitoring devices developed by device developers, EarlySense and Sibel, to accurately and
38 39 40	104	reliably measure vital signs in neonates (when compared to verified reference devices) and
41 42	105	to assess the feasibility, usability and acceptability of these devices for use in neonates in a
43 44 45	106	low-resource setting in Africa.
46 47 48	107	
49 50 51 52	108	METHODS AND ANALYSIS
53 54 55	109	Study design and setting
56 57 58	110	The primary objectives of this prospective, observational, facility-based research are: 1) to
59 60	111	assess agreement between repeat observations by the investigational device and the
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2 3	112	reference device for each relevant measurement parameter of interest based on a priori-
4 5		
6 7	113	determined accuracy threshold among neonates; 2) to compare clinical event detection
8 9	114	performance between the investigational device and the reference device; and 3) to
10 11 12 13 14	115	determine whether the investigational device is feasible, usable and acceptable to hospital
	116	administrators, healthcare providers and caregivers of neonates. Secondary objectives include:
15 16 17	117	1) assessing diagnostic performance for each relevant measurement parameter of interest
17 18 19	118	based on sensitivity, specificity, positive predictive value, and negative predictive value
20 21	119	compared to the reference device; 2) determining the downtime performance of the
22 23 24	120	investigational device; 3) determining the alarm rate (events/hour) and the number of
25 26	121	true/false alarms of the investigational device compared to the reference device; 4)
27 28 29	122	determining the delay time between the investigational device and the reference device in
30 31	123	true events; and 5) determining the number of adverse device effects (ADEs) and serious
32 33 34	124	adverse events (SAEs) during use of the investigational device.
35 36	125	Beginning in June 2019 and anticipated to last approximately 18 months in Nairobi, Kenya, this
37 38	126	research consists of two phases: 1) a verification and accuracy evaluation phase conducted at Aga
39 40 41	127	Khan University – Nairobi (AKU-N), a private, not-for-profit university teaching hospital with
42 43	128	a neonatal intensive care and high dependency units; and 2) a clinical feasibility phase
44 45 46	129	conducted at Pumwani Maternity Hospital (PMH), the largest referral maternity hospital in
47 48	130	sub-Saharan Africa with no neonatal intensive care or high dependency units.
49 50 51	131	Study participants
52 53	132	Up to 500 neonates, corrected age of \leq 28 days admitted for routine observation and care at
54 55 56	133	AKU-N and PMH are recruited by trained study staff during routine intake and screening
57 58	134	procedures. To avoid potential selection bias, neonates are screened for enrollment in a
59 60	135	sequential manner, as much as possible. Trained study staff assess the neonate for all

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30	inclusion and exclusion criteria (Table 1). Final eligibility determination is dependent on the
37	results of the medical history, clinical examination, appropriate understanding of the study
38	by the caregiver, and completion of the written informed consent process. A neonate may
39	be enrolled to the study more than once as long as they meet the eligibility criteria and the
40	caregiver(s) is willing to have the neonate participate.
41	For the feasibility, usability and acceptability assessment, hospital administrators and study
42	healthcare providers are enrolled if they are 18 years or older, involved in or aware of the
43	ETNA study, and have provided written informed consent. Caregivers may be enrolled if
44	they are 18 years or older, have a neonate enrolled in the study, and are willing to
45	participate in a 30-minute in-depth interview as well as direct observation while their
46	neonate is on or attached to the investigational device(s).
47	Investigational devices
48	Developed by Israeli-based EarlySense since 2009, the Insight system, released in 2016, is a
48 49	Developed by Israeli-based EarlySense since 2009, the Insight system, released in 2016, is a contact-free monitoring system comprised of a small piezoelectric sensor pad that can be
48 49 50	Developed by Israeli-based EarlySense since 2009, the Insight system, released in 2016, is a contact-free monitoring system comprised of a small piezoelectric sensor pad that can be placed under the patient's mattress, and is designed to measure and record a patient's
48 49 50 51	Developed by Israeli-based EarlySense since 2009, the Insight system, released in 2016, is a contact-free monitoring system comprised of a small piezoelectric sensor pad that can be placed under the patient's mattress, and is designed to measure and record a patient's heart rate (HR), respiratory rate (RR), motion, and sleep status. Information from the sensor
48 49 50 51 52	Developed by Israeli-based EarlySense since 2009, the Insight system, released in 2016, is a contact-free monitoring system comprised of a small piezoelectric sensor pad that can be placed under the patient's mattress, and is designed to measure and record a patient's heart rate (HR), respiratory rate (RR), motion, and sleep status. Information from the sensor pad, in combination with EarlySense's artificial intelligence analytics, is transmitted to a
48 49 50 51 52 53	Developed by Israeli-based EarlySense since 2009, the Insight system, released in 2016, is a contact-free monitoring system comprised of a small piezoelectric sensor pad that can be placed under the patient's mattress, and is designed to measure and record a patient's heart rate (HR), respiratory rate (RR), motion, and sleep status. Information from the sensor pad, in combination with EarlySense's artificial intelligence analytics, is transmitted to a monitor to provide alert indications and vital sign trends to healthcare providers so that
48 49 50 51 52 53 54	Developed by Israeli-based EarlySense since 2009, the Insight system, released in 2016, is a contact-free monitoring system comprised of a small piezoelectric sensor pad that can be placed under the patient's mattress, and is designed to measure and record a patient's heart rate (HR), respiratory rate (RR), motion, and sleep status. Information from the sensor pad, in combination with EarlySense's artificial intelligence analytics, is transmitted to a monitor to provide alert indications and vital sign trends to healthcare providers so that they can monitor changes in a patient's condition. Currently in use in hospitals,
48 49 50 51 52 53 54 55	Developed by Israeli-based EarlySense since 2009, the Insight system, released in 2016, is a contact-free monitoring system comprised of a small piezoelectric sensor pad that can be placed under the patient's mattress, and is designed to measure and record a patient's heart rate (HR), respiratory rate (RR), motion, and sleep status. Information from the sensor pad, in combination with EarlySense's artificial intelligence analytics, is transmitted to a monitor to provide alert indications and vital sign trends to healthcare providers so that they can monitor changes in a patient's condition. Currently in use in hospitals, rehabilitative centers, and nursing homes to measure vital signs in adults and children above
48 49 50 51 52 53 54 55 56	Developed by Israeli-based EarlySense since 2009, the Insight system, released in 2016, is a contact-free monitoring system comprised of a small piezoelectric sensor pad that can be placed under the patient's mattress, and is designed to measure and record a patient's heart rate (HR), respiratory rate (RR), motion, and sleep status. Information from the sensor pad, in combination with EarlySense's artificial intelligence analytics, is transmitted to a monitor to provide alert indications and vital sign trends to healthcare providers so that they can monitor changes in a patient's condition. Currently in use in hospitals, rehabilitative centers, and nursing homes to measure vital signs in adults and children above 10 kg, the device is modified for use in neonates as part of this study. The adult device
48 49 50 51 52 53 54 55 56 57	Developed by Israeli-based EarlySense since 2009, the Insight system, released in 2016, is a contact-free monitoring system comprised of a small piezoelectric sensor pad that can be placed under the patient's mattress, and is designed to measure and record a patient's heart rate (HR), respiratory rate (RR), motion, and sleep status. Information from the sensor pad, in combination with EarlySense's artificial intelligence analytics, is transmitted to a monitor to provide alert indications and vital sign trends to healthcare providers so that they can monitor changes in a patient's condition. Currently in use in hospitals, rehabilitative centers, and nursing homes to measure vital signs in adults and children above 10 kg, the device is modified for use in neonates as part of this study. The adult device received regulatory approval from the United States Federal Drug Administration (FDA) and

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3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19	159	RR and motion. No adverse events (AEs) related to the system have been reported during 10
	160	years of monitoring.
	161	Developed in 2019, the advanced neonatal epidermal (ANNE) system from Sibel, a
	162	technology company spun out from the Center of Bio-Integrated Electronics at
	163	Northwestern University in the United States, is a system of two time-linked soft and
	164	flexible sensors designed to measure and monitor vital signs including HR, RR, oxygen
	165	saturation (SpO ₂), and skin temperature in neonates. The chest sensor couples to the skin
20 21	166	via a hypo-allergenic, biocompatible hydrogel adhesive optimized for reduced peel force
22 23 24	167	upon removal, and the limb unit couples via a latex-free soft fabric wrap adaptable to a
25 26	168	range of foot sizes and anatomies. Information from the sensors are wirelessly transmitted
27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44	169	to a monitor or mobile device via encrypted Bluetooth™ for real-time streaming from a
	170	customized mobile software application as well as onboard memory storage on the sensors
	171	themselves. The device has been validated in more than 50 neonates in a neonatal care unit
	172	without AEs.
	173	Reference devices
	174	We are employing the Masimo Rad-97™ and the Spengler Tempo Easy Bleu devices as our
	175	reference devices for this study. The Masimo Rad-97™ provides continuous physiological —
45 46 47	176	monitoring of HR, RR, SpO2, and capnography. The Spengler Tempo Easy Bleu non-contact
47 48 49	177	infrared thermometer predicts core body temperature from the temporal artery
50 51 52	178	temperature.
53 54 55	179	Study procedures
57 58	180	Following completion of screening for eligibility, a study comprehension checklist, and
59 60	181	written informed consent, study staff perform procedures (Appendix I: Schedule of study

1 2		
2 3 4	182	procedures and evaluations) according to the most recently approved version of the
5 6 7 8 9	183	protocol (current version 1.1, June 18, 2019). Enrolled neonates are assigned a participant
	184	identification number; information is collected on socio-demographic characteristics,
10 11 12	185	current clinical status, medical history, medications; and a physical examination is
13 14	186	performed.
15 16 17	187	Prior to initiating the accuracy evaluation of each investigational device, verification of the
18 19 20	188	reference devices, Masimo Rad-97™ and Tempo Easy Bleu, is undertaken at AKU-N to
21 22	189	ensure they are robustly functional and to confirm their within subject repeatability and
23 24 25	190	accuracy compared to standard clinical measurements (e.g., manual, bedside
26 27	191	electrocardiography) for the relevant parameters of interest. Neonates enrolled during
28 29 30 31 32	192	reference device verification continue to receive local standard of care while being observed
	193	intermittently for vital signs collection for a minimum of 1 hour using the Masimo Rad-97™
33 34 35	194	and intermittent measurements with the Tempo Easy Bleu. Observations may include video
36 37	195	recordings of the neonate and the Masimo Rad-97™reference device monitor for later
38 39	196	review to facilitate manual count observations. The reference device measurements will be
40 41 42	197	compared to manual measurements, clinical monitor observations, and video-assisted
43 44	198	observations. Reliability information gathered from the reference devices is utilized to
45 46 47	199	determine specific Go/No Go criteria for each parameter and each investigational device.
48 49 50	200	Further evaluation of each investigational device only proceeds should these criteria be met.
51 52	201	Enrollment in the accuracy evaluation of the investigational devices, EarlySense Insight
53 54 55	202	system and Sibel ANNE system, is initiated at AKU-N to formally assess their accuracy
56 57	203	compared to the verified reference device using repeated observations. Enrolled neonates
58 59 60	204	continue to receive local standard of care while having vital signs collected from the

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2 3 4 5 6 7 8 9 10 11 12 13 14	205	reference device as well as one or both of the investigational devices. Placement of the
	206	investigational and reference devices is done in a manner so as not to interfere with the
	207	neonate's clinical care. Observations are collected for a minimum of 1 hour and potentially
	208	for the entire duration of their stay in the hospital. Observations may consist of videotaping
	209	and/or taking photos of the neonate during the observation period after obtaining informed
15 16 17	210	consent from the caregiver. Any photos or videos takes are identified by patient
17 18 19	211	identification number only and stored on a secure server until the analyses are completed
20 21	212	and destroyed following analyses. During observation, clinical status and any activities are
22 23 24	213	updated and recorded including type and duration of care activities (e.g., feeding, diaper
25 26	214	changes, bathing, kangaroo mother care, etc.), clinical procedures, interventions, therapies,
27 28 29 30 31 32 33 34 35 36 37 38 39 40 41	215	laboratory tests, medications, environmental features and exposures during hospitalization.
	216	The device placement, output, and signal quality are also monitored. In addition, the
	217	neonates are assessed for any safety issues. Agreement between the investigational and
	218	reference devices is determined using a priori-defined accuracy thresholds. Thresholds are
	219	determined largely based on repeated within and between subject observations during
	220	verification of the reference devices. This is complemented by previously published
42 43 44	221	international standards where available, and clinical expert consensus opinion as needed.
44 45 46	222	Two a priori-determined thresholds are determined: one lower threshold to allow the
47 48 40	223	device developer to optimize the device for retesting, and a second higher threshold to
49 50 51 52 53	224	allow the device to move on to the clinical feasibility phase of testing. A maximum of 5
	225	rounds of testing and retesting are permitted for each investigational device. Each round of
54 55 56	226	testing or retesting consists of using a cohort of 20 neonates. Should the lower threshold
57 58	227	not be reached for at least one parameter, no further testing of the investigational device is
59 60	228	performed. Thus, information collected during the accuracy evaluation along with the <i>a</i>

3 4 5	229	priori-determined Go/No Go criteria established during verification of the reference devices
5 6 7	230	define which, if any, of the investigational devices moves forward with additional rounds of
8 9 10	231	testing or into the clinical feasibility phase at PMH.
11 12 13	232	An investigational device advances to the clinical feasibility phase once the agreement for
14 15	233	the measurement parameters of interest exceed the higher accuracy threshold. Enrollment
16 17 18	234	in the clinical feasibility phase of the investigational devices occurs at PMH in up to 120
19 20	235	enrolled neonates who receive local standard of care while being monitored with the
21 22	236	reference device(s) and one or both of the investigational devices. Observations are
23 24 25	237	collected for a minimum of 1 hour and involve measurement of vital signs via the
26 27	238	investigational and reference devices and monitoring for any critical event (i.e., low or high
28 29 30	239	HR, RR, or temperature or oxygen desaturation and apnea). Agreement between repeated
31 32	240	observations from the investigational and reference devices as well as diagnostic
33 34 25	241	performance in clinical event detection is evaluated. Additional performance metrics such as
35 36 37	242	alarm rates, alarm delays and uptime\downtime are compared between the investigational
38 39	243	and reference devices. Participation in the study does not interfere with or unnecessarily
40 41 42 43	244	delay the clinical care of the neonates.
44 45	245	Throughout all phases of the research, the investigational devices are not used to inform
46 47 48	246	clinical care. During the clinical feasibility phase, ETNA site study staff and hospital
40 49 50	247	healthcare providers are blinded to the data collected from the investigational devices to
51 52	248	prevent interference with clinical care. The study site investigators are responsible for close
53 54 55	249	safety monitoring of all participating neonates, including assessing for and reporting adverse
56 57	250	device effects (e.g., erythema or edema at the investigational or reference device sensor
58 59 60	251	site) and/or serious adverse events (i.e., any adverse device effect resulting in permanent

2 3 4	252	skin damage). Any adverse device effects or serious adverse events will be treated until
5 6 7	253	resolution or stabilization, and may require removal of devices and withdrawal of the
, 8 9	254	neonate from the study if necessary. If withdrawn by the study team, any enrolled neonate
10 11 12	255	who completes at least one hour of monitoring will be included in the analysis and results.
13 14 15 16	256	Qualitative substudy
17 18	257	After written informed consent is received from the study participants, a mixed methods
19 20 21	258	evaluation and data collection through audio-recorded semi-structured in-depth interviews
22 23	259	and direct observations are conducted by trained qualitative study staff to assess the
24 25 26	260	feasibility, usability, and acceptability of the investigational devices for monitoring of
27 28	261	neonates in an African-setting. Questions around technology use, experience with
29 30 31	262	continuous monitoring devices, and specific to each investigational and reference device will
32 33	263	be asked and their use observed. All hospital administrators and study healthcare providers
34 35 26	264	may be involved in this portion of the study. Caregivers with a neonate enrolled in the study
36 37 38	265	may also be asked if they would like to participate in the qualitative portion of the study.
39 40 41 42	266	Sample size
43 44	267	A total of up to 500 neonates are enrolled. For the verification of the reference devices at
45 46 47	268	AKU-N, up to 30 neonates are enrolled. Once this initial testing and data collection of the
48 49	269	reference devices are complete, for the accuracy evaluation phase at AKU-N, up to 120
50 51 52	270	neonates per investigational device are enrolled. Sample size estimates for the verification
53 54	271	of the reference devices and the accuracy evaluation phase are based on the confidence
55 56 57	272	intervals (CIs) desired for the limits of agreement. Sample sizes of 100-200 typically provide
58 59 60	273	tight Cls. A sample of 20 neonates with 10 replications per neonate per device per round of

Page 16 of 28

1 2		
2 3 4	274	testing provides limits of agreement with 95% CIs +/- 0.24, calculated as
5 6 7	275	1.96*sqrt($3/(20*10)$), times the standard deviation of the paired differences. The paired
7 8 9	276	differences are from the reference device and manual measurements obtained during
10 11 12	277	verification of the reference device, and from the reference device and investigational
12 13 14	278	device measurements obtained during the accuracy evaluation phase. For the clinical
15 16	279	feasibility phase at PMH, up to 120 neonates per investigational device are enrolled. The
17 18 19	280	sample sizes for each phase have been selected to maximize the amount of information
20 21 22	281	collected within the confines of the available resources.
23 24 25	282	For the feasibility, usability, and acceptability assessment, the total sample size includes all
26 27	283	hospital administrators and study healthcare providers willing to participate and provide
28 29	284	consent as well as up to 30 caregivers willing to participate and provide consent study at
30 31 32	285	each site.
33 34 35 36	286	Data collection and quality assurance
37 38	287	Quantitative study data is collected by clinical study staff using designated source
39 40 41	288	documents as well as electronic or paper-based case report forms. Data is stored and
42 43	289	managed by a database developed via Research Electronic Data Capture (REDCap), a secure
44 45 46	290	web application. Continuous physiological data and event data are recorded from the
47 48	291	investigational and reference devices at least once a second. All electronic data are collected
49 50 51	292	wirelessly or via a wired connection from the investigational and reference devices to a
52 53	293	study laptop using custom software applications. Qualitative study data is collected using
54 55 56 57 58 59	294	paper-based forms and audio recordings which are subsequently transcribed for analysis.

1 2		
2 3 4	295	Clinical research data, including data collected from the investigational and reference
5 6 7	296	devices, are maintained through a combination of secure electronic data management
7 8 9	297	system and physical files with restricted access to ensure confidentiality. Two distinct study
10 11 12	298	databases are maintained separately: the primary study database and a database with
12 13 14	299	participating neonate's personally identifiable information. To ensure accuracy and
15 16	300	completeness, data is routinely reviewed by the investigators through quality assurance
17 18 19	301	reviews, audits, and evaluation of the study safety and progress. Guideline for Good Clinical
20 21	302	Practice (GCP)/ ISO 14155 compliance is followed to ensure accurate, reliable, and
22 23 24	303	consistent data collection.
25 26 27 28	304	Data management
29 30	305	Primary data management activities, which include de-identified investigational and
31 32 33	306	reference device data transfer using end-to-end encryption with two-factor authentication,
34 35	307	data entry and validation, data cleaning, database quality control, and disaster recovery
36 37 38	308	plans are undertaken at the study site and are overseen by the on-site data manager. Data
39 40	309	review and analysis, oversight and preparation of final study database is performed by the
41 42 43	310	investigators in collaboration with the study site. Data are maintained and stored securely in
44 45	311	databases hosted at the study site throughout the study and for at least 5 years after study
46 47 48	312	closure. All data management activities are in compliance with International Council on
49 50	313	Harmonization (ICH) GCP E6, sponsor organization, and institutional requirements for the
51 52 53	314	protection of children and confidentiality of personal and health information.
55 55 56 57 58 59	315	Outcomes

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316	We hypothesize that the investigational device is accurate and reliable compared to the
317	reference device for each relevant measurement parameter of interest among neonates
318	and is feasible, usable and acceptable for use in neonates in low-resource settings. The
319	primary endpoint and secondary endpoints are detailed in Table 2.
320	Statistical analyses
321	Every second of data is automatically graded as optimal, acceptable and unacceptable based
322	on predefined rules for each device and each measurement parameter of interest according
323	to the quality of the data for each measurement parameter of interest. The Masimo Rad-
324	97™ provides a signal quality index that is used to determine data quality for HR and SpO2.
325	A custom algorithm has been produced to determine the capnography signal quality index.
326	Each of the investigational devices also provides a signal quality index. The quality
327	thresholds are determined following verification of the reference devices. All comparisons
328	are performed from observations between two devices (or a single device during
329	verification). At least 10 observations of 60 seconds of optimal quality data in each neonate,
330	at least 5 minutes apart, are randomly selected for each measurement parameter of
331	interest from the full recording. For the clinical feasibility phase, accuracy comparisons use
332	optimal or acceptable data. At least 3 hours of recording to a maximum of 12 hours are used \sim
333	for the performance metrics such as alarm rates, alarm delays and uptime\downtime.
334	The repeatability of the reference device parameter estimates initially is assessed with the
335	intraclass correlation coefficient (ICC). Additional training or standardization of procedures
336	is performed to ensure at least good repeatability (ICC >0.7). This is followed by measuring
337	agreement between the repeated reference observations and between the manual, clinical
338	monitor and video-assisted methods and the reference observations using the methods

1 2		
2 3 4	339	described by Bland and Altman for replicated observations. ⁶ The agreement is reported as a
5 6 7	340	mean bias with 95% CIs and 95% limits of agreement. Graphical representation of the data is
8 9	341	assessed with agreement plots, Clark error grids, and Polar plots to identify extreme outliers
10 11 12	342	and significant data trends.
13 14 15	343	In the accuracy evaluation, the root mean square difference (RMSD) and ICC are calculated
16 17	344	for each measurement parameter of interest to compare the multiple repeated
18 19 20	345	observations between the investigational and reference devices. The agreement between
21 22	346	each investigational device and reference device(s) is then calculated using the methods
23 24 25	347	described by Bland and Altman for replicated observations. The agreement is reported as a
26 27	348	mean bias with 95% CIs and 95% limits of agreement. Graphical representation of the data is
28 29 30	349	be assessed with agreement plots, Clark error grids, and Polar plots to identify extreme
31 32	350	outliers, impact on clinical decisions, and significant data trends. An <i>a priori</i> -defined
33 34 35	351	accuracy margin for agreement is used as a threshold value to allow for decisions regarding
36 37 38	352	proceeding to additional testing.
39 40	353	In the clinical feasibility phase, agreement between each investigational device and
41 42 43	354	reference device(s) is assessed as in the accuracy evaluation phase. Event detection rates,
44 45	355	alarm rates, alarm delays and uptime/ downtime are summarized with means, medians,
46 47 48	356	standard deviations and intra-quartile ranges as appropriate. Summaries of sensitivity,
49 50	357	specificity, positive predictive values and negative predictive values comparing each
51 52	358	measurement parameter of interest in the investigational device(s) to the reference
55 54 55	359	device(s) are produced. Comparisons of binary events are assessed using Cohen's weighted
56 57	360	Kappa and McNemar's test. The non-inferiority of alarm rates, alarm delays and uptime/
58 59 60	361	downtime are evaluated based on pre-specified thresholds.

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362	Qualitative data are collected through in-depth interviews and/or semi-structured
363	questionnaires and analyzed to assess feasibility, usability, and acceptability of the
364	investigational devices among hospital administrators and healthcare providers, and
365	acceptability among caregivers of enrolled neonates. Questions that explore familiarity,
366	knowledge, perceptions, attitudes and behaviors regarding the devices are included. The
367	qualitative data is in narrative format and the results are descriptive. The questionnaires are
368	coded and analyzed using a codebook with identified themes, including feasibility of using
369	each investigational device, barriers and facilitators to use, and perceived value. Qualitative
370	data analysis software is used to organize, code, and analyze the qualitative data in an
371	iterative process. The study team starts by identifying an initial set of codes and themes
372	based on the categories from the interview guides. During the coding process, attention is
373	paid to identifying emergent issues and themes that are added to the codebook and
374	included in the analysis. Responses from the interviews are coded and discrepancies
375	discussed and resolved for the final analysis and theme identification.
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3//	ETHICS AND DISSEMINATION
378	Ethical approvals and consent
379	The study is conducted in accordance with the ICH GCP and the Declaration of Helsinki 2008.
380	The protocol and other relevant study documents study were approved by the Western
381	Institutional Review Board 20191102 (Puyallup, Washington, United States of America), and
382	the Aga Khan University Nairobi Research Ethics Committee 2019/REC-02 (v2)(Nairobi,
383	Kenya). Written informed consent is obtained in the local language by trained study staff

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3 4	384	from all eligible neonate's caregivers and for the qualitative substudy, from participating
5 6 7	385	hospital administrators, healthcare providers, and caregivers prior to enrollment. Potential
8 9	386	participants will have adequate time to ask questions and a comprehension checklist will be
10 11 12	387	administered to ensure participant understanding.
13 14 15 16	388	Possible risks
17 18	389	Caregivers may feel compelled to enroll in the study in order to receive care for their
19 20 21	390	neonate within a research setting, which may be perceived as of a higher quality than the
22 23	391	standard of care. In order to minimize the risk of coercion, during the informed consent
24 25 26	392	process, study staff emphasize that the neonate will receive the required medical care
20 27 28	393	whether enrolled in the study or not. Other potential risks to study participation may
29 30	394	include those associated with the placement and attachment of the investigational and
32 33	395	reference devices, and delayed medical management. Study staff are trained in the
34 35 26	396	appropriate placement of investigational and reference devices' sensors to minimize
30 37 38	397	discomfort to the neonates as well as to avoid interference with any assessment, treatment,
39 40	398	or intervention necessary for clinical care. There is a potential risk of skin irritation with the
41 42 43	399	ANNE sensor system and neonates will be closely monitored and treated for any AEs. Study
44 45	400	staff are also trained in integrating study procedures with clinical care and to always
46 47 48	401	prioritize clinical care above study procedures. Extreme care is taken to ensure that no
49 50	402	necessary treatment is delayed to accommodate study procedures.
51 52 53 54	403	Dissemination
55 56	404	We plan to disseminate study results in peer-reviewed journals and international
58 59 60	405	conferences, targeting those involved in the clinical care of neonates in low-resource

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3 4	406	settings as well as those who develop and advise on policies and guidelines in those settings.
5 6 7	407	The trial is registered with ClinicalTrials.gov (registration number NCT03920761).
8 9 10	408	Efforts towards rigorous protocol
12 13	409	Dedicated study staff trained in GCP, operation, use and maintenance of the investigational
14 15	410	and reference devices, and study-specific procedures follow neonates enrolled in the trial to
16 17 18	411	assure the protocol and standard operating procedures are followed and data are accurately
19 20	412	collected. Standardized study-specific training, supervision, and oversight are undertaken to
21 22 23	413	ensure quality, consistency, and harmonized trial procedures and implementation. Regular
24 25	414	monitoring is provided by the co-investigators to assess compliance with human subjects
26 27 28	415	and other research regulations and guidelines, adherence to the study protocol and
28 29 30	416	procedures, and quality and accuracy of data collected.
31 32 33 34	417	Limitations and bias
35 36 27	418	Limitations to this study and potential sources of bias include the sampling strategy, the
38 39	419	uncertainty inherent in the measurements from the reference devices, the limited
40 41	420	standardization of time of day of recording, and the inability to control the conditions and
42 43 44	421	standardize the context. Because there is a large variation in the various ages, weights, sizes,
45 46	422	disease states, clinical presentations, interventions received, and conditions of the
47 48 49	423	participating neonates, it is not possible to control for all these variables. Likewise, the
50 51	424	environment cannot be controlled, does not allow for complete standardization, and may
52 53 54	425	introduce additional sources of bias. These limitations may also be viewed as strengths.
55 56 57	426	DECLARATIONS
58 59	427	Authors' contributions ASG, EN, WM and MA designed the study and wrote the protocol.

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1 2		
2 3 4	428	RO, MW, GZ, RK, and SX reviewed and provided critical input to the study design and
5 6 7	429	protocol. ASG wrote the first draft of the manuscript, and EN and MA provided additional
, 8 9	430	input. All authors worked collaboratively, reviewed the manuscript, and made the decision
10 11 12	431	to submit the final manuscript for publication.
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15 16 17	433	application used to collect the high resolution data from the reference device.
18 19 20	434	Funding This work is supported by grants from the Bill & Melinda Gates Foundation
21 22 23	435	(OPP1203136) and the Save the Children Innovation Council. The authors had final
23 24 25	436	responsibility for the decision to submit this manuscript for publication.
26 27 28	437	Competing interests RK is employed by EarlySense Ltd. and SX is employed by Sibel Inc. All
29 30 31	438	other authors declare that they have no competing interests.
32 33	439	Ethics approval and consent to participate The study was approved by the Western
34 35 36	440	Institutional Review Board 20191102 (Puyallup, Washington, United States of America) and
37 38	441	the Aga Khan University Nairobi Research Ethics Committee2019/REC-02(v2) (Nairobi,
39 40 41	442	Kenya). Written informed consent is obtained by trained study staff from all eligible
42 43 44	443	children's caregivers prior to enrollment.
45 46	444	Consent for publication Not applicable.
47 48 49	445	Patient and public involvement Patients and the public were not involved in the design of,
50 51 52	446	recruitment to, or the conduct of the study.
53 54	447	Availability of data and materials Data will be made available on an open access platform
56 57	448	after the publication of the main manuscripts. Processes will be developed to facilitate data
58 59 60	449	sharing for scientific utilization in a collaborative manner.

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7

TABLES AND FIGURE LEGENDS

Table 1. Eligibility criteria

Inclusion	 Male or female peopate, corrected age of <28 days
	indic of female feofface, confected age of <u>2</u> 0 days.
criteria	Willingness and ability of neonate's caregiver to provide informed
	consent and to be available for follow-up for the planned duration
	of the study.
Exclusion	Receiving mechanical ventilation or continuous positive airway
criteria	pressure.
	• Skin abnormalities in the nasopharynx and/or oropharynx.
	Contraindication to application of skin sensors.
	Known arrhythmia.
	Presence of a congenital abnormality requiring major surgical
	intervention.
	Any medical or psychosocial condition or circumstance that, in the
	opinion of the investigators, would interfere with the conduct of
	the study or for which study participation might jeopardize the
	neonate's health.

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470 Table 2. Study endpoints

_						
Pri	lary endpoints					
•	Agreement of the relevant measurement parameters of interest between the					
	investigational device and the reference device at each observation.					
	Agreement of clinical event detection between the investigational device and the					
	eference device at each observation.					
	easibility, usability and acceptability of the investigational device among					
	nospital administrators and healthcare providers.					
	Acceptability of the investigational device among caregivers.					
Se	ondary endpoints					
•	Diagnostic performance of the investigational device to appropriately identify					
•	Diagnostic performance of the investigational device to appropriately identify					
	he following critical events:					
	 Low heart rate 					
	 High heart rate 					
	 Low respiratory rate 					
	 High respiratory rate 					
	 Oxygen desaturation 					
	o Apnea					
	 Low temperature 					
	 High temperature 					
	Downtime duration of the investigational device.					
	Alarm rate (events/hour and ratio of false positives to missed critical events of					
	the investigational device's alarms compared to the reference device's alarms.					

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3		Response time of the investigational device's alarms compared to the reference
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5		device's alarms for critical events
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9		• Proportion of neonates with adverse device effects and serious adverse events
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1 Appendix I: Schedule of study procedures and evaluations

Activity	Screening	Enrollment	Observation	Discharge
Eligibility assessment	x			
Informed consent and				
comprehension checklist	x	e.,		
Assign participant ID	X	000		
Demographics	X	х	10	
Medical history		Х	X	х
Maternal pregnancy history		Х	C	4
Medications use		Х		0
Placement of reference and/or investigational device(s)		х	х	
Collection of vital signs		X	X	X
Video tape recording and/or photographs			Х	
Track clinical care and non-study activities Safety assessment End of study questions Removal of investigational and/or reference device(s) 2	x x	X		
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Track clinical care and non-study activities Safety assessment End of study questions Removal of investigational and/or reference device(s) 2	x x	X		
activities		X		
Safety assessment End of study questions Removal of investigational and/or reference device(s) 2	X	x		
End of study questions		X		
Removal of investigational and/or reference device(s)		x		
reference device(s)		x		
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BMJ Open

Evaluation of noninvasive continuous physiological monitoring devices for neonates in Nairobi, Kenya: A research protocol

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13 14 15	5	Authors: Amy Sarah Ginsburg, ¹ * Evangelyn Nkwopara, ² William Macharia, ³ Roseline
16 17	6	Ochieng, ³ Mary Waiyego, ⁴ Guohai Zhou, ⁵ Roman Karasik, ⁶ Shuai Xu, ^{7,8} and J. Mark
18 19 20	7	Ansermino ⁹
21 22 23	8	
24 25 26	9	
27 28 29 30	10	¹ University of Washington, Seattle, Washington, USA
31 32 33	11	² Children's Healthcare of Atlanta, Atlanta, Georgia, USA
34 35 36 27	12	³ Aga Khan University, Nairobi, Kenya
37 38 39 40	13	⁴ Pumwani Maternity Hospital, Nairobi, Kenya
41 42 43	14	⁵ Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA
44 45 46	15	⁶ EarlySense Ltd., Ramat-Gan, Israel
47 48 49 50	16	⁷ Sibel Inc., Evanston, Illinois, USA
50 51 52 53	17	⁸ Northwestern University, Evanston, Illinois, USA
54 55 56	18	⁹ The University of British Columbia, Vancouver, Canada
57 58 59 60	19	

1			
2 3 4	20	* Corresponding aut	thor:
5 6 7 8	21	Mailing address:	University of Washington Clinical Trial Center
9 10 11	22		Building 29, Suite 250, 6200 NE 74 th Street
12 13 14 15	23		Seattle, WA, 98115, USA
16 17 18	24	Phone:	(206)616-8014
20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47			
48 49 50 51 52 53 54 55 56 57 58 59 60			2

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2	26	ABSTRACT
4 5		
6 7	27	
7 8 9	28	Introduction: Continuous physiological monitoring devices are often not available for
10 11 12	29	monitoring high-risk neonates in low-resource settings. Easy-to-use, noninvasive,
13 14	30	multiparameter, continuous physiological monitoring devices could be instrumental in
15 16 17	31	providing appropriate care and improving outcomes for high-risk neonates in these low-
18 19	32	resource settings.
20 21	33	Methods and Analysis: The purpose of this prospective, observational, facility-based
22 23		
24	34	evaluation is to provide evidence to establish whether two existing noninvasive,
25 26 27	35	multiparameter, continuous physiological monitoring devices developed by device
28 29 30	36	developers, EarlySense and Sibel, can accurately and reliably measure vital signs in neonates
31 32	37	(when compared to verified reference devices). We will also assess the feasibility, usability
33 34 35	38	and acceptability of these devices for use in neonates in low-resource settings in Africa. Up
36 37	39	to 500 neonates are enrolled in two phases: 1) a verification and accuracy evaluation phase at
38 39 40	40	Aga Khan University - Nairobi; and 2) a clinical feasibility phase at Pumwani Maternity Hospital in
41 42	41	Nairobi, Kenya. Both quantitative and qualitative data are collected and analyzed. Agreement
43 44	42	between the investigational and reference devices is determined using <i>a priori</i> -defined
45 46 47	43	accuracy thresholds.
48 49 50	44	Ethics and Dissemination: This trial was approved by the Aga Khan University Nairobi
51 52	45	Research Ethics Committee and the Western Institutional Review Board. We plan to
53 54 55	46	disseminate research results in peer-reviewed journals and international conferences.
56 57 58	47	ClinicalTrials.gov NCT03920761
59 60	48	

1 2		
3 4	49	Keywords: neonates, continuous physiological monitoring devices
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51	STRENGTHS AND LIMITATIONS OF THIS STUDY	
52	• This research consists of two phases, a verification and accuracy evaluation phase a	nd a clinical
53	feasibility phase, and evaluation of two novel, investigational, noninvasive, multip	arameter,
54	continuous physiological monitoring devices.	
55	• A verification of the reference devices is undertaken prior to initiating the ac	curacy
56	evaluation of the investigational devices to ensure the reference devices are	robustly
57	functional and to confirm their within subject repeatability and accuracy con	pare to
58	standard clinical measurements for the relevant parameters of interest.	
59	• Reliability information gathered from the reference devices is utilized to determine	ermine
60	specific <i>a priori</i> Go/No Go criteria for each parameter and each investigation	al device.
61	• As with all measurements, there is uncertainty inherent in the measurement	s from the
62	reference devices.	
63	Inability to control for the characteristics and conditions of the participating	neonates
64	and to standardize the environment and context are both strengths and limit	tations to
65	interpreting the results.	
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1 2 3	67	INTRODUCTION
4 5		
6 7	68	In 2017 globally,
8 9 10	69	28 days of life, w
11 12	70	or 2.5 million ne
13 14 15	71	mortality with ar
16 17	72	African countries
18 19 20	73	Development Go
21 22	74	live births by 203
23 24 25	75	neonates will die
25 26 27	76	for early detection
28 29 20	77	reduce current a
30 31 32 33	78	Multiparameter
34 35	79	identifying neon
36 37 38	80	automatic interp
39 40	81	treatment is suff
41 42	82	devices would be
43 44 45	83	is greatest. While
46 47	84	settings for those
48 49 50	85	to operate, maki
51 52	86	these barriers, it
53 54 55	87	optimized for use
55 56 57	88	independent, no
58 59	89	workload. This re
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7	INTRODUCTION	
8	In 2017 globally, 47% of all deaths in children under 5 years of age occurred within the first	
9	28 days of life, which translates to a neonatal mortality rate of 18 deaths per 1000 live births	
0	or 2.5 million newborn deaths. ¹ Sub-Saharan Africa bears the greatest burden of neonatal	
1	mortality with an estimated 1 million newborn deaths in 2017. Further efforts, especially in	
2	African countries, are needed to push progress towards achieving the Sustainable	
3	Development Goal (SDG) target of reducing global neonatal mortality to 12 deaths per 1000	
4	live births by 2030. ² Without accelerated improvements, it is projected that 1.8 million	
5	neonates will die in 2030. ³ Innovations in neonatal care, particularly technologies that allow	
6	for early detection and intervention for major morbidities, hold great promise in helping to	
7	reduce current and projected neonatal mortality rates.	
8	Multiparameter continuous physiological monitoring devices could be instrumental in	
9	identifying neonates at risk. We can then direct care provided for a neonate through	
0	automatic interpretations of vital signs that help identify critical events and determine if	
1	treatment is sufficient or insufficient, ultimately improving newborn outcomes. ⁴⁵ These	
2	devices would be most useful in low-resource settings where the need for such technologies	
3	is greatest. While continuous physiological monitoring is standard of care in high-resource	
4	settings for those who require it, the devices are expensive and require specialized training	
5	to operate, making them unsuitable for application in low-resource settings. To address	
6	these barriers, it is necessary to explore how these technologies can be adapted and/or	
7	optimized for use in low-resource settings. Ideally, the devices should be low cost, operator-	
8	independent, noninvasive and highly efficient in diagnostic performance and operator	
9	workload. This requires development of a robust testing platform that appropriately mimics	

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3 4	90	conditions common in African newborn or neonatal intensive care units that would allow
5 6 7	91	these type of technologies to be evaluated for feasibility and performance.
8 9 10	92	The Evaluation of Technologies for Neonates in Africa (ETNA) project was conceived with
11 12	93	the goal of advancing and supporting development, as well as evaluation, of select devices
13 14 15	94	for use in neonates in low-resource settings. By establishing a testing platform in an African
16 17	95	site, and working collaboratively with partners with expertise in device development and
18 19 20	96	evaluation and neonatal and child health, the project seeks to boost development and
20 21 22	97	optimization of promising newborn care devices that could be applied in low-resource
23 24	98	settings in Africa. We acknowledge the many challenges involved in implementing such
25 26 27	99	devices in low-resource settings (e.g., electricity and internet access, behavior change
28 29	100	communication, etc.), and the need to consider these challenges carefully prior to
30 31 32	101	introduction. The purpose of this initial research is to produce evidence regarding the
33 34	102	performance of two existing noninvasive, multiparameter, continuous physiological
35 36 27	103	monitoring devices developed by device developers, EarlySense and Sibel, to accurately and
37 38 39	104	reliably measure vital signs in neonates (when compared to verified reference devices) and
40 41 42	105	to assess the feasibility, usability and acceptability of these devices for use in neonates in a
42 43 44	106	low-resource setting in Africa.
45 46	107	
47 48 40		
49 50 51	108	METHODS AND ANALYSIS
52 53 54 55	109	Study design and setting
56 57	110	The primary objectives of this prospective, observational, facility-based research are: 1) to
58 59	111	assess agreement between repeat observations by the investigational device and the
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2 3 4	112	reference device for each relevant measurement parameter of interest based on a priori-
5 6 7 8 9	113	determined accuracy threshold among neonates; 2) to compare clinical event detection
	114	performance between the investigational device and the reference device; and 3) to
10 11	115	determine whether the investigational device is feasible, usable and acceptable to hospital
12 13 14	116	administrators, healthcare providers and caregivers of neonates. Secondary objectives include:
15 16	117	1) assessing diagnostic performance for each relevant measurement parameter of interest
17 18 19	118	based on sensitivity, specificity, positive predictive value, and negative predictive value
20 21	119	compared to the reference device; 2) determining the downtime performance of the
22 23 24	120	investigational device; 3) determining the alarm rate (events/hour) and the number of
25 26	121	true/false alarms of the investigational device compared to the reference device; 4)
27 28 29	122	determining the delay time between the investigational device and the reference device in
30 31	123	true events; and 5) determining the number of adverse device effects (ADEs) and serious
32 33 34	124	adverse events (SAEs) during use of the investigational device.
35 36	125	Beginning in June 2019 and anticipated to last approximately 18 months in Nairobi, Kenya, this
37 38 39	126	research consists of two phases: 1) a verification and accuracy evaluation phase conducted at Aga
40 41	127	Khan University – Nairobi (AKU-N), a private, not-for-profit university teaching hospital with
42 43 44	128	a neonatal intensive care and high dependency units; and 2) a clinical feasibility phase
45 46	129	conducted at Pumwani Maternity Hospital (PMH), the largest referral maternity hospital in
47 48 49	130	sub-Saharan Africa with no neonatal intensive care or high dependency units.
50 51	131	Study participants
52 53	132	Up to 500 neonates, corrected age of \leq 28 days admitted for routine observation and care at
55 56	133	AKU-N and PMH are recruited by trained study staff during routine intake and screening
57 58	134	procedures. To avoid potential selection bias, neonates are screened for enrollment in a
59 60	135	sequential manner, as much as possible. Trained study staff assess the neonate for all

1 2		
3 4	136	inclusion and exclusion criteria (Table 1). Final eligibility determination is dependent on the
5 6 7	137	results of the medical history, clinical examination, appropriate understanding of the study
, 8 9	138	by the caregiver, and completion of the written informed consent process. A neonate may
10 11	139	be enrolled to the study more than once as long as they meet the eligibility criteria and the
12 13 14	140	caregiver(s) is willing to have the neonate participate.
15 16	141	For the feasibility, usability and acceptability assessment, hospital administrators and study
17 18 19	142	healthcare providers are enrolled if they are 18 years or older, involved in or aware of the
20 21	143	ETNA study, and have provided written informed consent. Caregivers may be enrolled if
22 23 24	144	they are 18 years or older, have a neonate enrolled in the study, and are willing to
24 25 26	145	participate in a 30-minute in-depth interview as well as direct observation while their
27 28 20	146	neonate is on or attached to the investigational device(s).
29 30 31 32		
31 32	147	Investigational devices
31 32 33 34 35	147 148	Investigational devices Developed by Israeli-based EarlySense since 2009, the Insight system, released in 2016, is a
31 32 33 34 35 36 37	147 148 149	Investigational devices Developed by Israeli-based EarlySense since 2009, the Insight system, released in 2016, is a contact-free monitoring system comprised of a small piezoelectric sensor pad that can be
31 32 33 34 35 36 37 38 39 40	147 148 149 150	Investigational devices Developed by Israeli-based EarlySense since 2009, the Insight system, released in 2016, is a contact-free monitoring system comprised of a small piezoelectric sensor pad that can be placed under the patient's mattress, and is designed to measure and record a patient's
31 32 33 34 35 36 37 38 39 40 41 42	147 148 149 150 151	Investigational devices Developed by Israeli-based EarlySense since 2009, the Insight system, released in 2016, is a contact-free monitoring system comprised of a small piezoelectric sensor pad that can be placed under the patient's mattress, and is designed to measure and record a patient's heart rate (HR), respiratory rate (RR), motion, and sleep status. ⁶ Information from the
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 	147 148 149 150 151 152	Investigational devices Developed by Israeli-based EarlySense since 2009, the Insight system, released in 2016, is a contact-free monitoring system comprised of a small piezoelectric sensor pad that can be placed under the patient's mattress, and is designed to measure and record a patient's heart rate (HR), respiratory rate (RR), motion, and sleep status. ⁶ Information from the sensor pad, in combination with EarlySense's artificial intelligence analytics, is transmitted
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 40 	147 148 149 150 151 152 153	Investigational devices Developed by Israeli-based EarlySense since 2009, the Insight system, released in 2016, is a contact-free monitoring system comprised of a small piezoelectric sensor pad that can be placed under the patient's mattress, and is designed to measure and record a patient's heart rate (HR), respiratory rate (RR), motion, and sleep status. ⁶ Information from the sensor pad, in combination with EarlySense's artificial intelligence analytics, is transmitted to a monitor to provide alert indications and vital sign trends to healthcare providers so that
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 	147 148 149 150 151 152 153 154	Investigational devices Developed by Israeli-based EarlySense since 2009, the Insight system, released in 2016, is a contact-free monitoring system comprised of a small piezoelectric sensor pad that can be placed under the patient's mattress, and is designed to measure and record a patient's heart rate (HR), respiratory rate (RR), motion, and sleep status. ⁶ Information from the sensor pad, in combination with EarlySense's artificial intelligence analytics, is transmitted to a monitor to provide alert indications and vital sign trends to healthcare providers so that they can monitor changes in a patient's condition. Currently in use in hospitals,
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 	147 148 149 150 151 152 153 154 155	Investigational devices Developed by Israeli-based EarlySense since 2009, the Insight system, released in 2016, is a contact-free monitoring system comprised of a small piezoelectric sensor pad that can be placed under the patient's mattress, and is designed to measure and record a patient's heart rate (HR), respiratory rate (RR), motion, and sleep status. ⁶ Information from the sensor pad, in combination with EarlySense's artificial intelligence analytics, is transmitted to a monitor to provide alert indications and vital sign trends to healthcare providers so that they can monitor changes in a patient's condition. Currently in use in hospitals, rehabilitative centers, and nursing homes to measure vital signs in adults and children above
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 	147 148 149 150 151 152 153 154 155 156	Investigational devices Developed by Israeli-based EarlySense since 2009, the Insight system, released in 2016, is a contact-free monitoring system comprised of a small piezoelectric sensor pad that can be placed under the patient's mattress, and is designed to measure and record a patient's heart rate (HR), respiratory rate (RR), motion, and sleep status. ⁶ Information from the sensor pad, in combination with EarlySense's artificial intelligence analytics, is transmitted to a monitor to provide alert indications and vital sign trends to healthcare providers so that they can monitor changes in a patient's condition. Currently in use in hospitals, rehabilitative centers, and nursing homes to measure vital signs in adults and children above 10 kg, the device is modified for use in neonates as part of this study. The adult device
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 	147 148 149 150 151 152 153 154 155 156 157	Investigational devices Developed by Israeli-based EarlySense since 2009, the Insight system, released in 2016, is a contact-free monitoring system comprised of a small piezoelectric sensor pad that can be placed under the patient's mattress, and is designed to measure and record a patient's heart rate (HR), respiratory rate (RR), motion, and sleep status. ⁶ Information from the sensor pad, in combination with EarlySense's artificial intelligence analytics, is transmitted to a monitor to provide alert indications and vital sign trends to healthcare providers so that they can monitor changes in a patient's condition. Currently in use in hospitals, rehabilitative centers, and nursing homes to measure vital signs in adults and children above 10 kg, the device is modified for use in neonates as part of this study. The adult device received regulatory approval from the United States Federal Drug Administration (FDA) and

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2 3 4	159	RR and motion. No adverse events (AEs) related to the system have been reported during 10
5 6 7	160	years of monitoring.
7 8 9 10 11 12 13 14	161	Developed in 2019, the advanced neonatal epidermal (ANNE) system from Sibel, a
	162	technology company spun out from the Center of Bio-Integrated Electronics at
	163	Northwestern University in the United States, is a system of two time-linked soft and
15 16	164	flexible sensors designed to measure and monitor vital signs including HR, RR, oxygen
17 18 19	165	saturation (SpO ₂), and skin temperature in neonates. ⁷ The chest sensor couples to the skin
20 21	166	via a hypo-allergenic, biocompatible hydrogel adhesive optimized for reduced peel force
22 23 24	167	upon removal, and the limb unit couples via a latex-free soft fabric wrap adaptable to a
25 26	168	range of foot sizes and anatomies. Information from the sensors are wirelessly transmitted
27 28 29	169	to a monitor or mobile device via encrypted Bluetooth™ for real-time streaming from a
30 31	170	customized mobile software application as well as onboard memory storage on the sensors
32 33 34	171	themselves. The device has been validated in more than 50 neonates in a neonatal care unit
35 36	172	without AEs.
37 38 30	173	Reference devices
40 41 42	174	We are employing the Masimo Rad-97™ and the Spengler Tempo Easy Bleu devices as our
43 44	175	reference devices for this study. The Masimo Rad-97™ provides continuous physiological
45 46 47	176	monitoring of HR, RR, SpO2, and capnography. The Spengler Tempo Easy Bleu non-contact
48 49	177	infrared thermometer predicts core body temperature from the temporal artery
50 51 52	178	temperature.
53 54 55	179	Study procedures
56 57 58	180	Following completion of screening for eligibility, a study comprehension checklist, and
59 60	181	written informed consent, study staff perform procedures (Appendix I: Schedule of study

1 2		
2 3 4	182	procedures and evaluations) according to the most recently approved version of the
5 6 7	183	protocol (current version 1.1, June 18, 2019). Enrolled neonates are assigned a participant
8 9	184	identification number; information is collected on socio-demographic characteristics,
10 11 12	185	current clinical status, medical history, medications; and a physical examination is
13 14	186	performed.
15 16 17	187	Prior to initiating the accuracy evaluation of each investigational device, verification of the
18 19 20	188	reference devices, Masimo Rad-97™ and Tempo Easy Bleu, is undertaken at AKU-N to
21 22	189	ensure they are robustly functional and to confirm their within subject repeatability and
23 24 25	190	accuracy compared to standard clinical measurements (e.g., manual, bedside
26 27	191	electrocardiography) for the relevant parameters of interest. Neonates enrolled during
28 29 30	192	reference device verification continue to receive local standard of care while being observed
31 32	193	intermittently for vital signs collection for a minimum of 1 hour using the Masimo Rad-97™
33 34 35	194	and intermittent measurements with the Tempo Easy Bleu. Observations may include video
36 37	195	recordings of the neonate and the Masimo Rad-97™reference device monitor for later
39 40	196	review to facilitate manual count observations. The reference device measurements will be
41 42 43	197	compared to manual measurements, clinical monitor observations, and video-assisted
44 45	198	determine specific Ge/Ne Ge criteria for each parameter and each investigational device
46 47 48	200	Eurther evaluation of each investigational device only proceeds should these criteria be met
49 50	200	
51 52 53	201	Enrollment in the accuracy evaluation of the investigational devices, EarlySense Insight
54 55	202	system and Sibel ANNE system, is initiated at AKU-N to formally assess their accuracy
50 57 58	203	compared to the verified reference device using repeated observations. Enrolled neonates
59 60	204	continue to receive local standard of care while having vital signs collected from the

1		
2 3 4	205	reference device as well as one or both of the investigational devices. Placement of the
5 6 7 8 9 10 11 12 13 14	206	investigational and reference devices is done in a manner so as not to interfere with the
	207	neonate's clinical care. Observations are collected for a minimum of 1 hour and potentially
	208	for the entire duration of their stay in the hospital. Observations may consist of videotaping
	209	and/or taking photos of the neonate during the observation period after obtaining informed
15 16 17	210	consent from the caregiver. Any photos or videos takes are identified by patient
17 18 19	211	identification number only and stored on a secure server until the analyses are completed
20 21	212	and destroyed following analyses. During observation, clinical status and any activities are
22 23 24	213	updated and recorded including type and duration of care activities (e.g., feeding, diaper
25 26	214	changes, bathing, kangaroo mother care, etc.), clinical procedures, interventions, therapies,
27 28 29	215	laboratory tests, medications, environmental features and exposures during hospitalization.
30 31	216	The device placement, output, and signal quality are also monitored. In addition, the
32 33 34	217	neonates are assessed for any safety issues. Agreement between the investigational and
35 36	218	reference devices is determined using <i>a priori</i> -defined accuracy thresholds. Thresholds are
37 38 39	219	determined largely based on repeated within and between subject observations during
40 41	220	verification of the reference devices. This is complemented by previously published
42 43	221	international standards where available, and clinical expert consensus opinion as needed.
44 45 46	222	Two a priori-determined thresholds are determined: one lower threshold to allow the
47 48	223	device developer to optimize the device for retesting, and a second higher threshold to
49 50 51 52 53	224	allow the device to move on to the clinical feasibility phase of testing. A maximum of 5
	225	rounds of testing and retesting are permitted for each investigational device. Each round of
54 55 56	226	testing or retesting consists of using a cohort of 20 neonates. Should the lower threshold
57 58	227	not be reached for at least one parameter, no further testing of the investigational device is
59 60	228	performed. Thus, information collected during the accuracy evaluation along with the <i>a</i>

3 4 5	229	priori-determined Go/No Go criteria established during verification of the reference devices
5 6 7	230	define which, if any, of the investigational devices moves forward with additional rounds of
8 9 10	231	testing or into the clinical feasibility phase at PMH.
11 12 13	232	An investigational device advances to the clinical feasibility phase once the agreement for
14 15	233	the measurement parameters of interest exceed the higher accuracy threshold. Enrollment
16 17 18	234	in the clinical feasibility phase of the investigational devices occurs at PMH in up to 120
19 20	235	enrolled neonates who receive local standard of care while being monitored with the
21 22 23	236	reference device(s) and one or both of the investigational devices. Observations are
24 25	237	collected for a minimum of 1 hour and involve measurement of vital signs via the
26 27 28	238	investigational and reference devices and monitoring for any critical event (i.e., low or high
29 30	239	HR, RR, or temperature or oxygen desaturation and apnea). Agreement between repeated
31 32 33	240	observations from the investigational and reference devices as well as diagnostic
34 35	241	performance in clinical event detection is evaluated. Additional performance metrics such as
36 37 38	242	alarm rates, alarm delays and uptime\downtime are compared between the investigational
39 40	243	and reference devices. Participation in the study does not interfere with or unnecessarily
41 42 43	244	delay the clinical care of the neonates.
44 45	245	Throughout all phases of the research, the investigational devices are not used to inform
46 47 48	246	clinical care. During the clinical feasibility phase, ETNA site study staff and hospital
49 50	247	healthcare providers are blinded to the data collected from the investigational devices to
51 52 53	248	prevent interference with clinical care. The study site investigators are responsible for close
54 55	249	safety monitoring of all participating neonates, including assessing for and reporting adverse
56 57 58	250	device effects (e.g., erythema or edema at the investigational or reference device sensor
59 60	251	site) and/or serious adverse events (i.e., any adverse device effect resulting in permanent

2 3 4	252	skin damage). Any adverse device effects or serious adverse events will be treated until
5 6 7	253	resolution or stabilization, and may require removal of devices and withdrawal of the
7 8 9	254	neonate from the study if necessary. If withdrawn by the study team, any enrolled neonate
10 11 12	255	who completes at least one hour of monitoring will be included in the analysis and results.
13 14 15 16	256	Qualitative substudy
10 17 18	257	After written informed consent is received from the study participants, a mixed methods
19 20 21	258	evaluation and data collection through audio-recorded semi-structured in-depth interviews
22 23	259	and direct observations are conducted by trained qualitative study staff to assess the
24 25 26	260	feasibility, usability, and acceptability of the investigational devices for monitoring of
27 28	261	neonates in an African-setting. Questions around technology use, experience with
29 30 31	262	continuous monitoring devices, and specific to each investigational and reference device will
32 33	263	be asked and their use observed. All hospital administrators and study healthcare providers
34 35	264	may be involved in this portion of the study. Caregivers with a neonate enrolled in the study
36 37 38	265	may also be asked if they would like to participate in the qualitative portion of the study.
39 40 41 42	266	Sample size
43 44	267	A total of up to 500 neonates are enrolled. For the verification of the reference devices at
45 46 47	268	AKU-N, up to 30 neonates are enrolled. Once this initial testing and data collection of the
48 49	269	reference devices are complete, for the accuracy evaluation phase at AKU-N, up to 120
50 51 52	270	neonates per investigational device are enrolled. Sample size estimates for the verification
53 54	271	of the reference devices and the accuracy evaluation phase are based on the confidence
55 56 57	272	intervals (CIs) desired for the limits of agreement. Sample sizes of 100-200 typically provide
58 59 60	273	tight Cls. A sample of 20 neonates with 10 replications per neonate per device per round of

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4	 ³ 274 testing provides limits of agreement with 95% CIs +/- 0.24, calculated as 			
 5 6 275 1.96*sqrt(3/(20*10)), times the standard deviation of the paired d 		1.96*sqrt(3/(20*10)), times the standard deviation of the paired differences. The paired		
8 9	276	differences are from the reference device and manual measurements obtained during		
10 11	277	verification of the reference device, and from the reference device and investigational		
12 13 14	278	device measurements obtained during the accuracy evaluation phase. For the clinical		
15 16	279	feasibility phase at PMH, up to 120 neonates per investigational device are enrolled. The		
17 18 19	280	sample sizes for each phase have been selected to maximize the amount of information		
20 21 22	281	collected within the confines of the available resources.		
23 24 25	282	For the feasibility, usability, and acceptability assessment, the total sample size includes all		
26 27	283	hospital administrators and study healthcare providers willing to participate and provide		
28 29	284	consent as well as up to 30 caregivers willing to participate and provide consent study at		
30 31 32	285	each site.		
32				
32 33 34 35 36	286	Data collection and quality assurance		
32 33 34 35 36 37 38	286 287	Data collection and quality assurance Quantitative study data is collected by clinical study staff using designated source		
32 33 34 35 36 37 38 39 40 41	286 287 288	Data collection and quality assurance Quantitative study data is collected by clinical study staff using designated source documents as well as electronic or paper-based case report forms. Data is stored and		
32 33 34 35 36 37 38 39 40 41 42 43	286 287 288 289	Data collection and quality assurance Quantitative study data is collected by clinical study staff using designated source documents as well as electronic or paper-based case report forms. Data is stored and managed by a database developed via Research Electronic Data Capture (REDCap), a secure		
32 33 34 35 36 37 38 39 40 41 42 43 44 45 46	286 287 288 289 290	Data collection and quality assurance Quantitative study data is collected by clinical study staff using designated source documents as well as electronic or paper-based case report forms. Data is stored and managed by a database developed via Research Electronic Data Capture (REDCap), a secure web application. Continuous physiological data and event data are recorded from the		
 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 	286 287 288 289 290 291	Data collection and quality assurance Quantitative study data is collected by clinical study staff using designated source documents as well as electronic or paper-based case report forms. Data is stored and managed by a database developed via Research Electronic Data Capture (REDCap), a secure web application. Continuous physiological data and event data are recorded from the investigational and reference devices at least once a second. All electronic data are collected		
 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 	286 287 288 289 290 291 291	Data collection and quality assurance Quantitative study data is collected by clinical study staff using designated source documents as well as electronic or paper-based case report forms. Data is stored and managed by a database developed via Research Electronic Data Capture (REDCap), a secure web application. Continuous physiological data and event data are recorded from the investigational and reference devices at least once a second. All electronic data are collected wirelessly or via a wired connection from the investigational and reference devices to a		
 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 	286 287 288 289 290 291 291 292 293	Data collection and quality assurance Quantitative study data is collected by clinical study staff using designated source documents as well as electronic or paper-based case report forms. Data is stored and managed by a database developed via Research Electronic Data Capture (REDCap), a secure web application. Continuous physiological data and event data are recorded from the investigational and reference devices at least once a second. All electronic data are collected wirelessly or via a wired connection from the investigational and reference devices to a study laptop using custom software applications. Qualitative study data is collected using		
32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 950 51 52 53 54 55 56 57	286 287 288 289 290 291 292 293 293 294	Data collection and quality assurance Quantitative study data is collected by clinical study staff using designated source documents as well as electronic or paper-based case report forms. Data is stored and managed by a database developed via Research Electronic Data Capture (REDCap), a secure web application. Continuous physiological data and event data are recorded from the investigational and reference devices at least once a second. All electronic data are collected wirelessly or via a wired connection from the investigational and reference devices to a study laptop using custom software applications. Qualitative study data is collected using paper-based forms and audio recordings which are subsequently transcribed for analysis.		

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1 2		
2 3 4	295	Clinical research data, including data collected from the investigational and reference
5 6 7	296	devices, are maintained through a combination of secure electronic data management
8 9	297	system and physical files with restricted access to ensure confidentiality. Two distinct study
10 11 12	298	databases are maintained separately: the primary study database and a database with
13 14	299	participating neonate's personally identifiable information. To ensure accuracy and
15 16 17	300	completeness, data is routinely reviewed by the investigators through quality assurance
17 18 19	301	reviews, audits, and evaluation of the study safety and progress. Guideline for Good Clinical
20 21	302	Practice (GCP)/ ISO 14155 compliance is followed to ensure accurate, reliable, and
22 23 24	303	consistent data collection.
25 26 27 28	304	Data management
29 30	305	Primary data management activities, which include de-identified investigational and
31 32 33	306	reference device data transfer using end-to-end encryption with two-factor authentication,
34 35	307	data entry and validation, data cleaning, database quality control, and disaster recovery
36 37 38	308	plans are undertaken at the study site and are overseen by the on-site data manager. Data
39 40	309	review and analysis, oversight and preparation of final study database is performed by the
41 42 43	310	investigators in collaboration with the study site. Data are maintained and stored securely in
44 45	311	databases hosted at the study site throughout the study and for at least 5 years after study
46 47 48	312	closure. All data management activities are in compliance with International Council on
49 50	313	Harmonization (ICH) GCP E6, sponsor organization, and institutional requirements for the
51 52 53	314	protection of children and confidentiality of personal and health information.
54 55 56 57 58 59	315	Outcomes

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316	We hypothesize that the investigational device is accurate and reliable compared to the
317	reference device for each relevant measurement parameter of interest among neonates
318	and is feasible, usable and acceptable for use in neonates in low-resource settings. The
319	primary endpoint and secondary endpoints are detailed in Table 2.
320	Statistical analyses
321	Every second of data is automatically graded as optimal, acceptable and unacceptable based
322	on predefined rules for each device and each measurement parameter of interest according
323	to the quality of the data for each measurement parameter of interest. The Masimo Rad-
324	97™ provides a signal quality index that is used to determine data quality for HR and SpO2.
325	A custom algorithm has been produced to determine the capnography signal quality index.
326	Each of the investigational devices also provides a signal quality index. The quality
327	thresholds are determined following verification of the reference devices. All comparisons
328	are performed from observations between two devices (or a single device during
329	verification). At least 10 observations of 60 seconds of optimal quality data in each neonate,
330	at least 5 minutes apart, are randomly selected for each measurement parameter of
331	interest from the full recording. For the clinical feasibility phase, accuracy comparisons use
332	optimal or acceptable data. At least 3 hours of recording to a maximum of 12 hours are used \sim
333	for the performance metrics such as alarm rates, alarm delays and uptime\downtime.
334	The repeatability of the reference device parameter estimates initially is assessed with the
335	intraclass correlation coefficient (ICC). Additional training or standardization of procedures
336	is performed to ensure at least good repeatability (ICC >0.7). This is followed by measuring
337	agreement between the repeated reference observations and between the manual, clinical
338	monitor and video-assisted methods and the reference observations using the methods

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2 3 4	339	described by Bland and Altman for replicated observations. ⁸ The agreement is reported as a
5 6 7	340	mean bias with 95% CIs and 95% limits of agreement. Graphical representation of the data is
8 9	341	assessed with agreement plots, Clark error grids, and Polar plots to identify extreme outliers
10 11 12	342	and significant data trends.
13 14 15	343	In the accuracy evaluation, the root mean square difference (RMSD) and ICC are calculated
16 17	344	for each measurement parameter of interest to compare the multiple repeated
18 19 20	345	observations between the investigational and reference devices. The agreement between
21 22 22	346	each investigational device and reference device(s) is then calculated using the methods
23 24 25	347	described by Bland and Altman for replicated observations. The agreement is reported as a
26 27 28	348	mean bias with 95% CIs and 95% limits of agreement. Graphical representation of the data is
28 29 30	349	be assessed with agreement plots, Clark error grids, and Polar plots to identify extreme
31 32	350	outliers, impact on clinical decisions, and significant data trends. An <i>a priori</i> -defined
33 34 35	351	accuracy margin for agreement is used as a threshold value to allow for decisions regarding
36 37 38	352	proceeding to additional testing.
39 40	353	In the clinical feasibility phase, agreement between each investigational device and
41 42 43	354	reference device(s) is assessed as in the accuracy evaluation phase. Event detection rates,
44 45	355	alarm rates, alarm delays and uptime/ downtime are summarized with means, medians,
46 47 48	356	standard deviations and intra-quartile ranges as appropriate. Summaries of sensitivity,
49 50	357	specificity, positive predictive values and negative predictive values comparing each
51 52 53	358	measurement parameter of interest in the investigational device(s) to the reference
54 55	359	device(s) are produced. Comparisons of binary events are assessed using Cohen's weighted
56 57 58	360	Kappa and McNemar's test. The non-inferiority of alarm rates, alarm delays and uptime/
59 60	361	downtime are evaluated based on pre-specified thresholds.

362	Qualitative data are collected through in-depth interviews and/or semi-structured
363	questionnaires and analyzed to assess feasibility, usability, and acceptability of the
364	investigational devices among hospital administrators and healthcare providers, and
365	acceptability among caregivers of enrolled neonates. Questions that explore familiarity,
366	knowledge, perceptions, attitudes and behaviors regarding the devices are included. The
367	qualitative data is in narrative format and the results are descriptive. The questionnaires are
368	coded and analyzed using a codebook with identified themes, including feasibility of using
369	each investigational device, barriers and facilitators to use, and perceived value. Qualitative
370	data analysis software is used to organize, code, and analyze the qualitative data in an
371	iterative process. The study team starts by identifying an initial set of codes and themes
372	based on the categories from the interview guides. During the coding process, attention is
373	paid to identifying emergent issues and themes that are added to the codebook and
374	included in the analysis. Responses from the interviews are coded and discrepancies
375	discussed and resolved for the final analysis and theme identification.
376	
377	ETHICS AND DISSEMINATION
378	Ethical approvals and consent
379	The study is conducted in accordance with the ICH GCP and the Declaration of Helsinki 2008.
380	The protocol and other relevant study documents study were approved by the Western
381	Institutional Review Board 20191102 (Puyallup, Washington, United States of America), and
382	the Aga Khan University Nairobi Research Ethics Committee 2019/REC-02 (v2)(Nairobi,
383	Kenya). Written informed consent is obtained in the local language by trained study staff

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3 4	384	from all eligible neonate's caregivers and for the qualitative substudy, from participating
5 6 7	385	hospital administrators, healthcare providers, and caregivers prior to enrollment. Potential
8 9	386	participants will have adequate time to ask questions and a comprehension checklist will be
10 11 12	387	administered to ensure participant understanding.
13 14 15 16	388	Possible risks
17 18	389	Caregivers may feel compelled to enroll in the study in order to receive care for their
19 20 21	390	neonate within a research setting, which may be perceived as of a higher quality than the
22 23	391	standard of care. In order to minimize the risk of coercion, during the informed consent
24 25 26	392	process, study staff emphasize that the neonate will receive the required medical care
20 27 28	393	whether enrolled in the study or not. Other potential risks to study participation may
29 30 21	394	include those associated with the placement and attachment of the investigational and
31 32 33	395	reference devices, and delayed medical management. Study staff are trained in the
34 35 26	396	appropriate placement of investigational and reference devices' sensors to minimize
30 37 38	397	discomfort to the neonates as well as to avoid interference with any assessment, treatment,
39 40	398	or intervention necessary for clinical care. There is a potential risk of skin irritation with the
41 42 43	399	ANNE sensor system and neonates will be closely monitored and treated for any AEs. Study
44 45	400	staff are also trained in integrating study procedures with clinical care and to always
46 47 48	401	prioritize clinical care above study procedures. Extreme care is taken to ensure that no
49 50	402	necessary treatment is delayed to accommodate study procedures.
51 52 53 54	403	Dissemination
55 56	404	We plan to disseminate study results in peer-reviewed journals and international
57 58 59 60	405	conferences, targeting those involved in the clinical care of neonates in low-resource

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3 4	406	settings as well as those who develop and advise on policies and guidelines in those settings.
5 6 7	407	The trial is registered with ClinicalTrials.gov (registration number NCT03920761).
8 9 10	408	Efforts towards rigorous protocol
12 13	409	Dedicated study staff trained in GCP, operation, use and maintenance of the investigational
14 15	410	and reference devices, and study-specific procedures follow neonates enrolled in the trial to
16 17 18	411	assure the protocol and standard operating procedures are followed and data are accurately
19 20	412	collected. Standardized study-specific training, supervision, and oversight are undertaken to
21 22 23	413	ensure quality, consistency, and harmonized trial procedures and implementation. Regular
24 25	414	monitoring is provided by the co-investigators to assess compliance with human subjects
26 27 28	415	and other research regulations and guidelines, adherence to the study protocol and
28 29 30	416	procedures, and quality and accuracy of data collected.
31 32 33 34	417	Limitations and bias
35 36 27	418	Limitations to this study and potential sources of bias include the sampling strategy, the
37 38 39	419	uncertainty inherent in the measurements from the reference devices, the limited
40 41	420	standardization of time of day of recording, and the inability to control the conditions and
42 43 44	421	standardize the context. Because there is a large variation in the various ages, weights, sizes,
45 46	422	disease states, clinical presentations, interventions received, and conditions of the
47 48 49	423	participating neonates, it is not possible to control for all these variables. Likewise, the
50 51	424	environment cannot be controlled, does not allow for complete standardization, and may
52 53 54	425	introduce additional sources of bias. These limitations may also be viewed as strengths.
55 56 57	426	DECLARATIONS
58 59	427	Authors' contributions ASG, EN, WM and MA designed the study and wrote the protocol.

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2 3 4	428	RO, MW, GZ, RK, and SX reviewed and provided critical input to the study design and
5 6 7	429	protocol. ASG wrote the first draft of the manuscript, and EN and MA provided additional
, 8 9	430	input. All authors worked collaboratively, reviewed the manuscript, and made the decision
10 11 12	431	to submit the final manuscript for publication.
13 14	432	Acknowledgments We would like to thank Dustin Dunsmuir who wrote the IAP logger
15 16 17	433	application used to collect the high resolution data from the reference device.
18 19 20	434	Funding This work is supported by grants from the Bill & Melinda Gates Foundation
21 22 23	435	(OPP1203136) and the Save the Children Innovation Council. The authors had final
23 24 25	436	responsibility for the decision to submit this manuscript for publication.
26 27 28	437	Competing interests RK is employed by EarlySense Ltd. and SX is employed by Sibel Inc. All
29 30 31	438	other authors declare that they have no competing interests.
32 33	439	Ethics approval and consent to participate The study was approved by the Western
34 35 36	440	Institutional Review Board 20191102 (Puyallup, Washington, United States of America) and
37 38 30	441	the Aga Khan University Nairobi Research Ethics Committee2019/REC-02(v2) (Nairobi,
40 41	442	Kenya). Written informed consent is obtained by trained study staff from all eligible
42 43 44	443	children's caregivers prior to enrollment.
45 46	444	Consent for publication Not applicable.
47 48 49	445	Patient and public involvement Patients and the public were not involved in the design of,
50 51 52	446	recruitment to, or the conduct of the study.
53 54	447	Availability of data and materials Data will be made available on an open access platform
56 57	448	after the publication of the main manuscripts. Processes will be developed to facilitate data
58 59 60	449	sharing for scientific utilization in a collaborative manner.

450 TABLES AND FIGURE LEGENDS

451 Table 1. Eligibility criteria

Eligibility criteria	
Inclusion	• Male or female neonate, corrected age of ≤28 days.
criteria	• Willingness and ability of neonate's caregiver to provide informed
	consent and to be available for follow-up for the planned duration
	of the study.
Exclusion	Receiving mechanical ventilation or continuous positive airway
criteria	pressure.
	• Skin abnormalities in the nasopharynx and/or oropharynx.
	Contraindication to application of skin sensors.
	Known arrhythmia.
	Presence of a congenital abnormality requiring major surgical
	intervention.
	• Any medical or psychosocial condition or circumstance that, in the
	opinion of the investigators, would interfere with the conduct of
	the study or for which study participation might jeopardize the
	neonate's health.

453 Table 2. Study endpoints

Pri	mary endpoints
•	Agreement of the relevant measurement parameters of interest between the
	investigational device and the reference device at each observation.
•	Agreement of clinical event detection between the investigational device and the
	reference device at each observation.
•	Feasibility, usability and acceptability of the investigational device among
	hospital administrators and healthcare providers.
•	Acceptability of the investigational device among caregivers.
Se	condary endpoints
•	Diagnostic performance of the investigational device to appropriately identify
	the following critical events:
	 Low heart rate
	 High heart rate
	 Low respiratory rate
	 High respiratory rate
	 Oxygen desaturation
	o Apnea
	 Low temperature
	 High temperature
•	Downtime duration of the investigational device.
•	Alarm rate (events/hour and ratio of false positives to missed critical events of
	the investigational device's alarms compared to the reference device's alarms.

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3 4		Response time of the investigational device's alarms compared to the reference
5 6 7		device's alarms for critical events.
7 8 9		Proportion of neonates with adverse device effects and serious adverse events
10 11		resulting in skin damage.
12 13	454	
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1 Appendix I: Schedule of study procedures and evaluations

Activity	Screening	Enrollment	Observation	Discharge
Eligibility assessment	x			
Informed consent and				
comprehension checklist	x			
		6		
Assign participant ID	X	6		
Demographics	X	X	1	
Medical history		х	x	х
Maternal pregnancy history		Х	C	4
Medications use		х		0
Placement of reference and/or		x	x	
investigational device(s)		~	~	
Collection of vital signs		Х	X	Х
Video tape recording and/or			v	
photographs			^	

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ck clinical care and non-study		v	x
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noval of investigational and/or			
erence device(s)			X