1. Biological vulnerability to extreme heat in maternal and child health application

Reference number	UNS143276
Applicant name	Prof Matthew Chersich
Title of application	Investigating the Biological pathways from HEAT exposure to preterm birth and other adverse maternal and child health outcomes in South Africa (the Bio-HEAT study)
Total amount requested	£2,000,000.00

2. Application summary

Application title
Investigating the Biological pathways from HEAT exposure to preterm birth and other adverse maternal and child health outcomes in South Africa (the Bio-HEAT study)

Proposed duration of funding (months)
42

Proposed start date	01/04/2023

Administering organisation type: Select the relevant administering organisation type.	Company

Name of administering organisation If your application is successful, this is the organisation that will be responsible for administering the award (including receiving the funds).
Wits Health Consortium (Pty) Ltd

Lead applicant's address at host organisation If your application is successful, we will use this address in your award letter.	
Department/Division	Climate and Health Directorate
Organisation	Wits Reproductive Health and HIV Institute
Street	31 Princess of Wales Terrace
City/Town	Parktown, Johannesburg
Postcode/Zipcode	2193
Country	South Africa

Pre-submission

Research subject area Select the most relevant area, based on the key aims of the research. This information is used to report on our funding.
Population and Public Health

Are you applying as an individual researcher or with coapplicants?	With coapplicants

3. Proposal summary

Proposal summary
Provide a summary of your proposed research, including key goals.

Approximately 190 studies have documented linkages between heat exposure, and adverse maternal and child health outcomes. Understanding the underlying biological vulnerabilities that explain these linkages is especially important given rising global temperatures and the urgent need for adaptive interventions. Applying transdisciplinary research in Johannesburg, South Africa, we will follow 200 women from the second trimester until one-year postpartum, together with their infant. Exposure to heat and other environmental factors will be tracked continuously through personal temperature monitors and geospatial variables at fine resolution. Our primary aim is to document linkages between heat exposure and inflammatory pathways that precede preterm birth. We will test the hypothesis that heat exposure triggers maternal inflammation by analysing epigenetic changes leading to inflammatory cytokine protein and gene expression. We also investigate the pathophysiology of thermoregulation and hydration in labour, focusing on potential protective mechanisms. Lastly, using breastmilk samples and isotope techniques, we assess whether heat exposure alters breastmilk composition and volume. Qualitative research with a sub-sample of women will explore psycho-social influences and help shape the putative pathways. Lastly, we will construct conceptual frameworks and Graphical Causal Models delineating pathways of biological vulnerability and potential protective mechanisms. Public engagement and communication underscore all study activities.

4. The proposal

Describe your programme of work. Ensure that you provide any further additional information requested on the call's webpage or by your Wellcome contact. In your description make sure you include:

- Aims and key deliverables;
- Background and justification;
- Details of the planned activities;
- Timetable and milestones (as appropriate).

If more than one organisation will be involved in the project, indicate what work will be undertaken at each organisation.

Pre-submission

1. Aims and deliverables

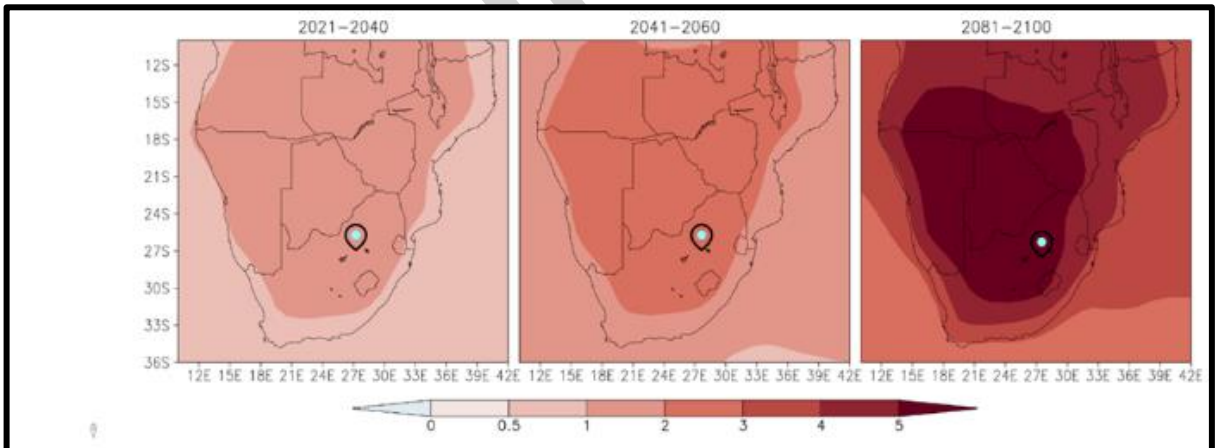
1.1 The Biological HEAT-exposure (Bio-HEAT) study aims to:

A. Define biological pathways and related biomarkers linking heat exposure to adverse clinical outcomes during pregnancy, intrapartum and postpartum
B. Develop conceptual frameworks depicting biological vulnerability to heat exposure during pregnancy, intrapartum and postpartum
C. Identify potential protective interventions at critical junctures on biological pathways

1.2 We will deliver research outputs on relationships between heat exposure and biological vulnerability to preterm birth, heat stress in labour and breastfeeding. Additional deliverables include progressively-refined conceptual frameworks depicting biological vulnerability to heat during pregnancy, intrapartum, and postpartum, taking into account perspectives of women. We will identify potential protective interventions, especially intrapartum.

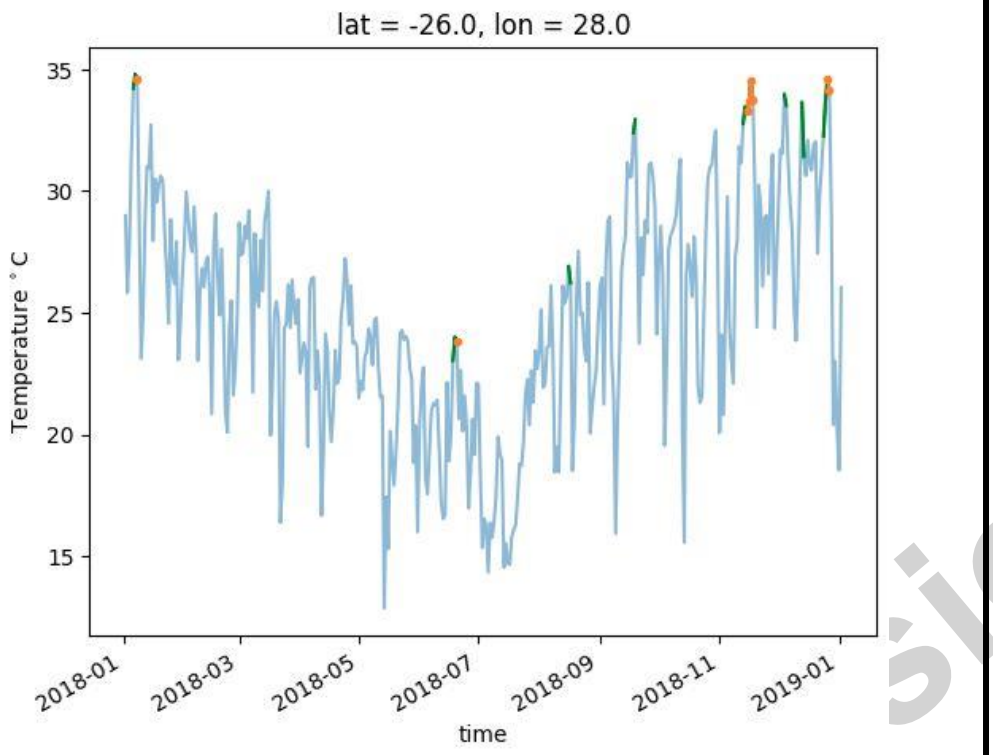
2. Background and study justification

2.1 Climate change in Africa is especially concerning as it is occurring in areas that are already naturally warm and dry, with highly variable rainfall [1]. Southern Africa in particular is a climate-change hotspot, with more frequent heatwaves of unprecedented intensity and temperatures in the interior rising at around twice the global rate[2, 3]. The country's interior is projected to become drastically warmer (Figure below)[1], as seen in a recent heat wave in Johannesburg (Additional Table 1, and line graph below)[4].



Projected change in average annual temperature as per the ensemble average of 30 different CGCMs that contributed to the 6th IPCC Assessment Report, for the periods 2021-2040 (near-future), 2041-2060 (mid-future) and 2081-2100 (far-future), relative to the baseline period 1979-2014, under the low-mitigation scenation SSP5-8.5

Submissio



Green lines signal days when the TMax exceeds the 95th percentile.
Orange lines are heatwaves (Tmax exceeds 95th percentile for ≥3 days

2.2 Pregnant women and infants in Africa are particularly vulnerable to climate change, with the highest risks among women and infants living in informal urban settlements or low-cost housing, as described by Chersich in the IPCC 6th Assessment Report[5].

2.3 In two commentaries[6, 7] and an expert group meeting report[8], we sum available evidence indicating that the biological impacts of heat on maternal and child health are mediated principally through three mechanisms: inflammatory responses, the overwhelming of thermoregulatory capacity, and dehydration. The predominating mediator may vary over gestation, in labour and postpartum.

2.4 Heat exposure in the first trimester is linked to increased rates of congenital anomalies (see systematic review by Chersich of 13 studies[9], and of hypertensive disorders of pregnancy as assessed in 26 studies[10], including a study in Johannesburg[11]. However, most women enrol at antenatal clinic after the first trimester, limiting the potential for protective interventions. Therefore, we focus on late pregnancy, labour, and postpartum, addressing one Research Question in each stage, consisting of one biological pathway and outcome selected based on our empirical research, updated systematic review, and the public health significance of the outcome. To ensure the proposal included the most recent evidence, we updated our systematic review on 1 November 2022 (PROSPERO CRD 42019140136 and CRD 42018118113).

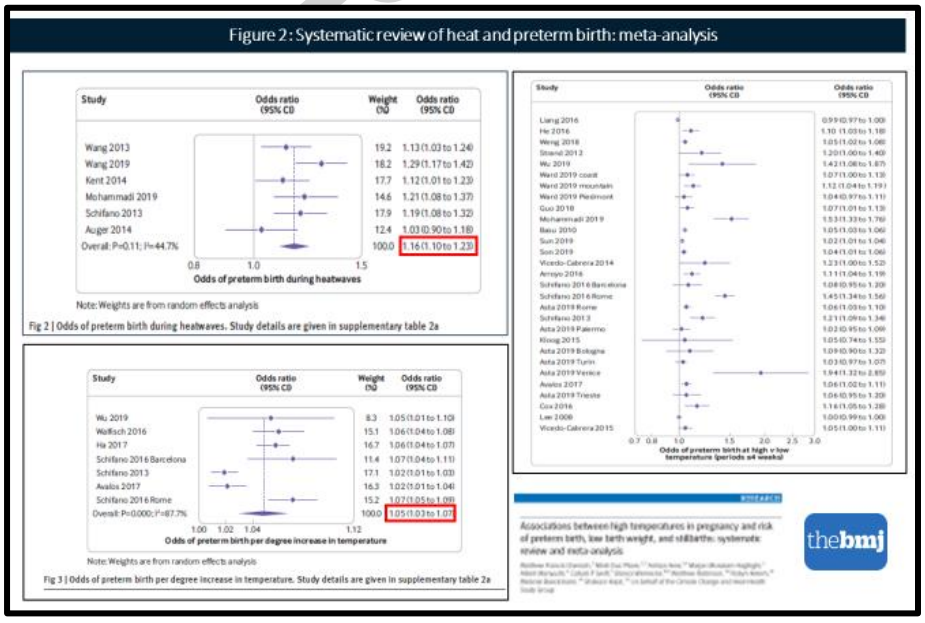
2.5 The contribution of psycho-social vulnerability to adverse maternal and infant health outcomes in our setting should not be underestimated[12]. Almost a quarter of pregnant women in our site have post-traumatic stress disorder (23%), 19% express suicidality, 19% have depression, and 27% have postpartum depression[13-15]. Much of this mental ill-health is linked to high levels of intimate partner violence and experiences of child abuse in this setting[16]. Alcohol use during pregnancy is common in South Africa, as shown in work involving Chersich and Urban[17-20], and is linked with prematurity. Consumption and violence rise exponentially with temperature[21]. We will collect qualitative data on the social-mental-physical health nexus as experienced by our participants, to contextualise and refine our findings on heat and poor maternal health outcomes.

3. Biological pathways in pregnancy: heat exposure, immune-inflammatory responses and preterm birth

"[In the heat], you can deliver a baby who has not reached its time." (Community Health Volunteer, Kenya). CHAMNHA study[22]

3.1 Preterm birth, the leading cause of under-five mortality worldwide, affects around 15-20% of births in Africa[23]. Few children born preterm in Africa have access to appropriate care and risks for death, or long-term health, social and economic sequalae are extremely high.

3.2 The Bio-HEAT team has documented clinically-significant heat impacts on pregnant women through a series of systematic reviews and empirical studies[9, 11, 24, 25]. Linkages between heat exposure and preterm birth are the most commonly described of all heat-health outcomes in pregnancy (33.9; 63 of all 186 studies on heat-health outcomes in pregnancy as of 1 November 2022), suggesting that the outcome is especially heat sensitive.



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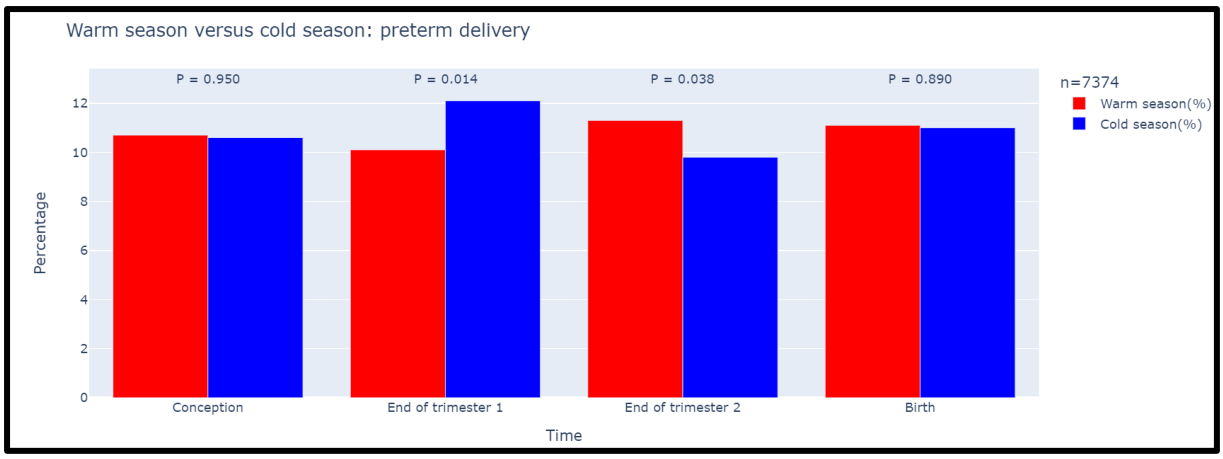
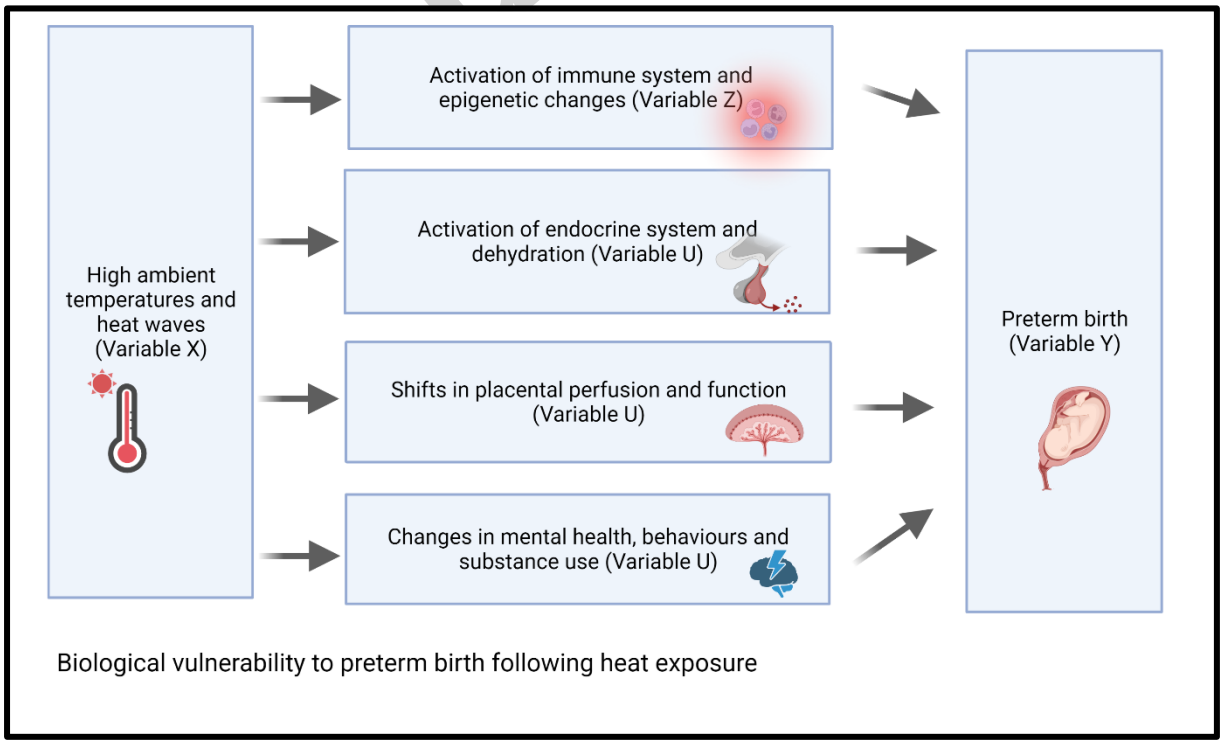


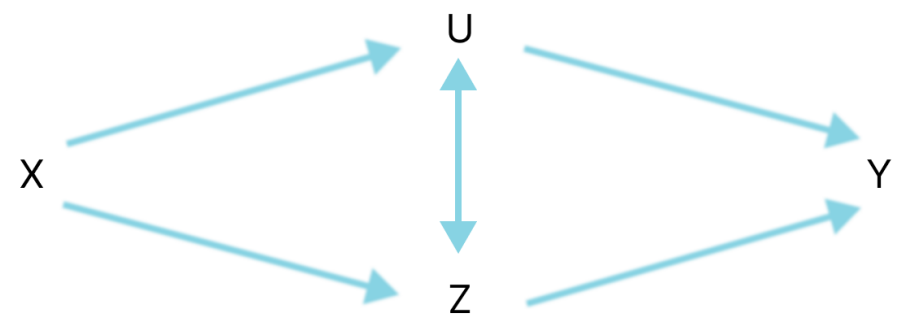
3.3 Preterm birth can be considered an 'early triggering birth event' caused by increased inflammatory events that breaks maternal-foetal tolerance and accelerates the ''immune clock'' of pregnancy[refs]. Inflammation is driven by various pro-inflammatory cytokines which we posit originates from alterations in gene expression due to epigenetic modifications. Heat exposure is one likely environmental driver of these changes, resulting in altered RNA expression and consequent immune activation. These changes cause heightened oxidative stress and a pro-parturient environment as supported by animal model studies[26, 27], Additionally, around 10 studies show that exposure to high temperatures *in utero* has life-long sequelae[10], likely due to epigenetic changes.

3.4 Our primary hypothesis, presented in a putative Graphical Causal Model, draws on three commentaries by the Bio-HEAT team[6-8]. Specifically, we will test whether exposure to the highest temperature quartile compared to the lowest (TMax, lag0_2 days; Variable X) is linked with raised pro-inflammatory cytokines using a combination of gene expression and secreted cytokine measurements (Pathway XZ). We will use Interleukin-6 protein as a representative marker (Variable Z), measured as weeks 18 and 28 gestation. In separate causal pathway analyses, we will assess links between IL-6 (Variable Z) and preterm birth (Variable Y), independent of heat exposure. We will use RNAseq complement measurements of secreted cytokines throughout pregnancy.



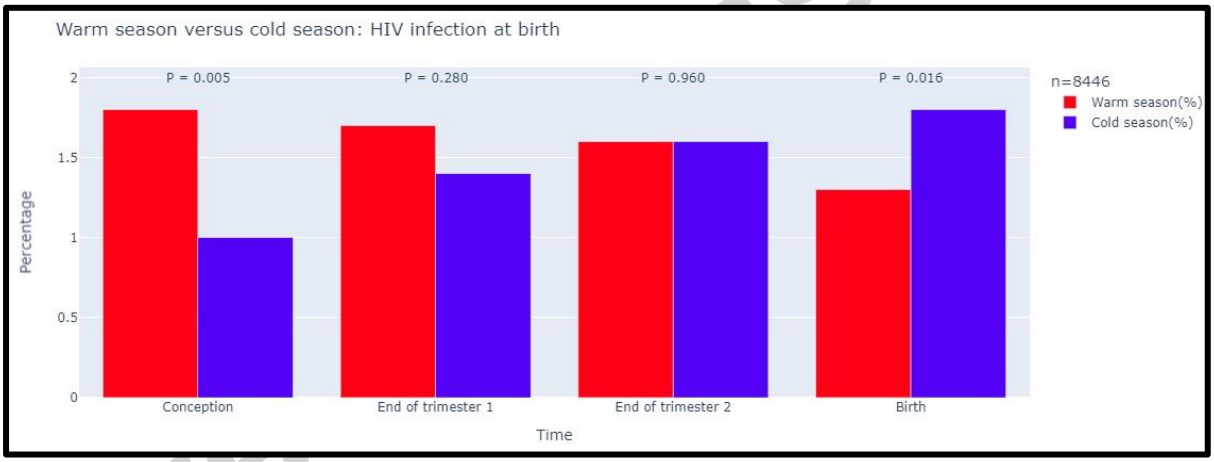
Biological vulnerability to preterm birth following heat exposure

Submission



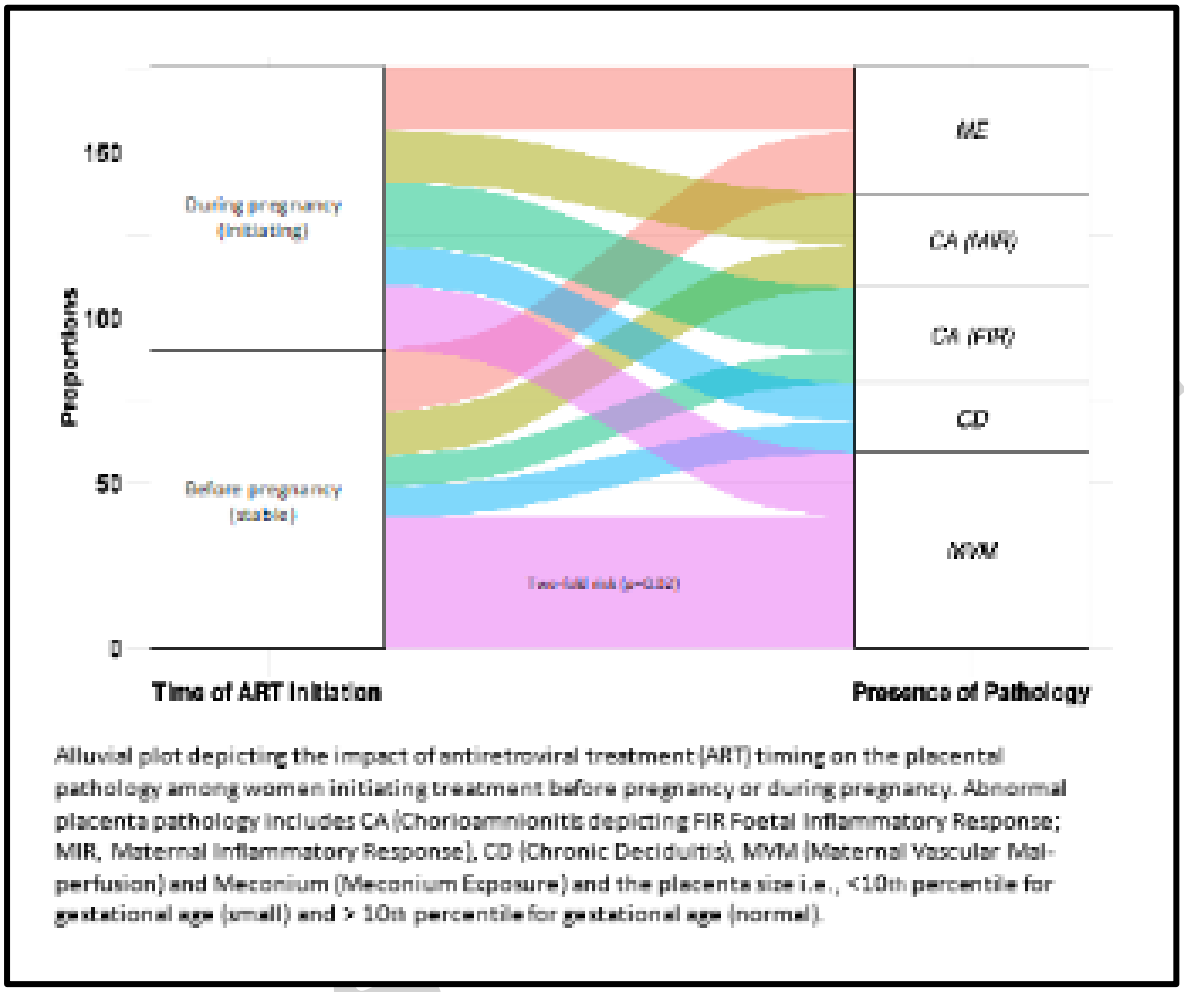
Directed Acyclic Graph. X=heat exposure. Z=mediator variable on pathway XZY. U=confounding or mediator variables

3.5 Aside from an activated immune system, many interacting factors (Variables U) have been implicated in preterm birth and need to be accounted for in the analysis. For example, high ambient temperatures can interrupt endocrine system function, increasing oxidative stress, inflammation, and the release of heat-shock proteins[28, 29]. Pregnant women with HIV infection may be especially at risk for heat exposure, as suggested by Chersich[30], and by data at the study site (Figure below).



Pre-submission

3.6 Women taking long-term antiretroviral treatment are high risk for maternal vascular malperfusion (Figure below), which is strongly associated with preterm birth, as shown by Gray[31].



Alluvial plot depicting the impact of antiretroviral treatment (ART) timing on the placental pathology among women initiating treatment before pregnancy or during pregnancy. Abnormal placenta pathology includes CA (Chorioamnionitis depicting FIR Foetal Inflammatory Response; MIR, Maternal Inflammatory Response), CD (Chronic Deciduitis), MVM (Maternal Vascular Malperfusion) and Meconium (Meconium Exposure) and the placenta size i.e., <10th percentile for gestational age (small) and > 10th percentile for gestational age (normal).

4. Biological pathways in labour: heat exposure, overwhelmed thermoregulation and dehydration

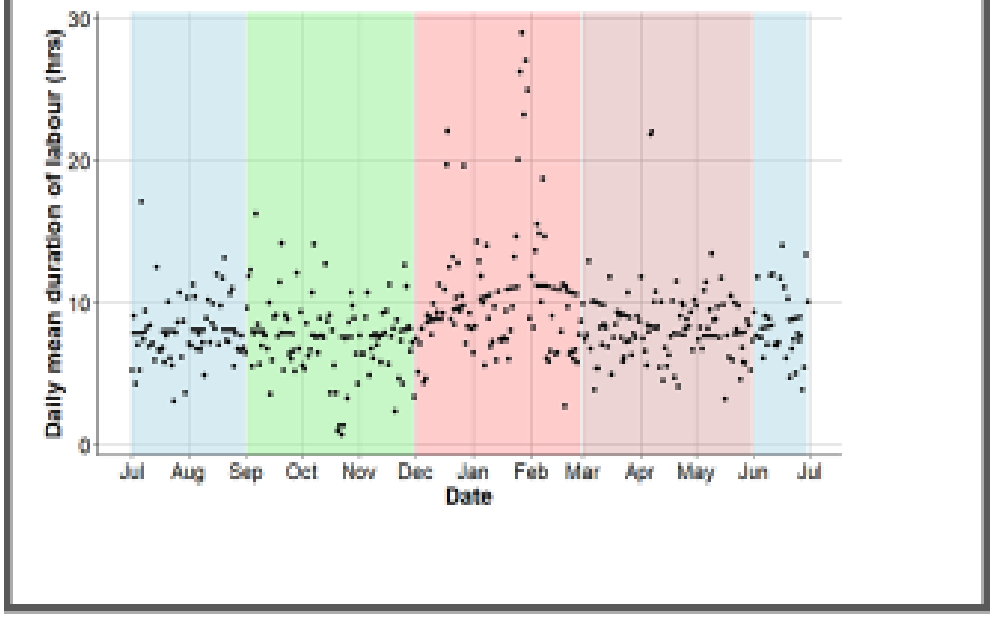
"[During labour], the temperature was very high, [there was] pain and discomfort…you feel the body has changed" (Postnatal woman, Kenya; CHAMNHA study)[22]

4.1 Africa has the highest rates of maternal mortality globally. Most deaths are due to haemorrhage, hypertensive disorders or sepsis[32], each of which are exacerbated by dehydration and heat exposure[10].

4.2 In normal labour, maternal temperature increases by about 0.02°C per hour, but at a considerably faster rate among women who are obese or have had epidural analgesia[33]. Endogenous thermal load from heat generated by the major exertion of labour and childbirth may overwhelm the maternal thermoregulatory mechanisms during labour, making it difficult to maintain normothermia, (Variable U) with major consequences for the foetus. Foetal temperature is consistently 0.3-0.5°C higher than the maternal core temperature[34], and can rise to dangerous levels if maternal temperatures increase. Maternal hyperthermia around childbirth increases the odds of neonatal brain injuries 2.5-fold[35]. Additionally, heat exposure can lead to increased uterine contractions, foetal tachycardia, foetal distress and Group B streptococcus infections[6].

4.3 Around 40% of women may have hypovolaemic dehydration during labour, even during periods with normal temperatures (Variable Z)[36]. This carries substantial risks for electrolyte imbalances and endothelial, oxidative, and inflammatory sequelae[37], potentially overwhelming already burdened cardiovascular and renal systems during labour.

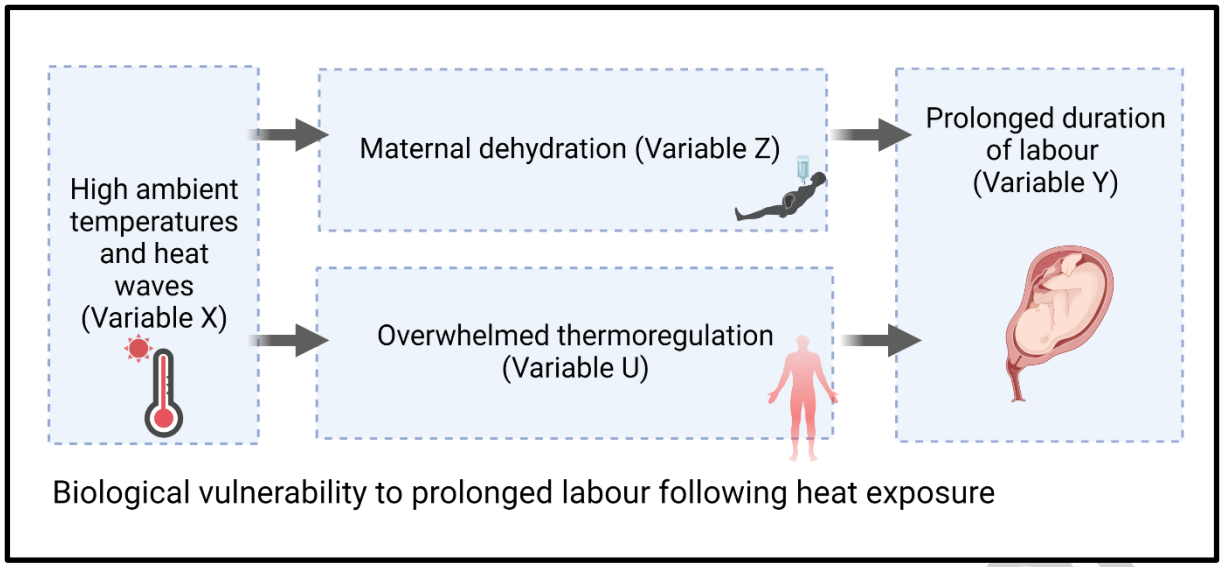
4.4 Women who are heat exposed and dehydrated during labour may have an increased duration of labour (Variable Y), as suggested by analyses in Johannesburg and elsewhere[10].



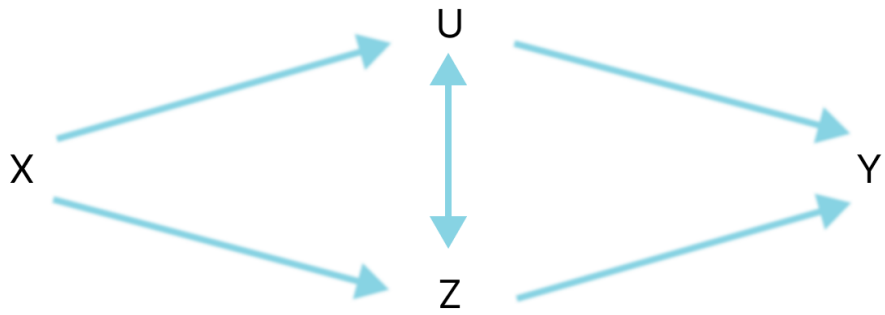
Provisional analysis of 7996 birth records in Johannesburg. Mean duration of labour with fitted natural cubic spline (*df*=6). Median duration in summer=7.7 hours (IQR=1.8-13.8), winter=6.4 hours (IQR=1.3-12.4), spring=6.3 hours (IQR=1.2-12.0) and autumn=6.2 hours (IQR=1.3-12.3. Wilcoxin signed rank test p<0.001). Summer counts of emergency Caesarean section due to foetal distress=396 (21% of births) versus winter=292 (14% of births). Chi-square p<0.001 (figure not shown). Weather data source: Tutiempo.net

4.5 Much is already known about effective interventions to reduce the direct impacts of heat exposure in high-risk groups. Concerted support for hydration during labour is already recommended by WHO in guidance led by Hofmeyr, for example[38]. We believe that withholding such interventions to test a biological pathway is unethical.

4.6 Adaptation interventions often centre on space cooling and hydration support[39]. We will contribute to evidence on biological vulnerability during labour by addressing the 'reversibility' criteria of causality[40]. In our second Research Question, we will determine whether low-cost, low-emission space cooling and provision of cool water in bottles can reduce dehydration during labour (urine specific gravity >1.015), compared to dehydration among non-study participants in the labour ward (n=15,000/year). Separate exploratory causal pathway analysis will assess links between personal temperature and labour duration, where hydration is potentially a mediating variable (Variable UZY).



Biological vulnerability to prolonged labour following heat exposure



Directed Acyclic Graph. X=heat exposure. Z=mediator variable on pathway XZY. U=confounding or mediator variables

5. Biological pathways in infancy: reduced breastfeeding and infant dehydration

''When there is more heat, the baby is uncomfortable to breastfeed…It is really a problem.'' (Male spouse, Kenya). "You will see the baby touching the breast and keep on crying because of the heat" (Traditional birth attendant, Kenya; CHAMNHA study)[22]

5.1 Infant mortality rates are highest in Africa, with many deaths related to dehydration (Variable Y)and gastroenteritis.

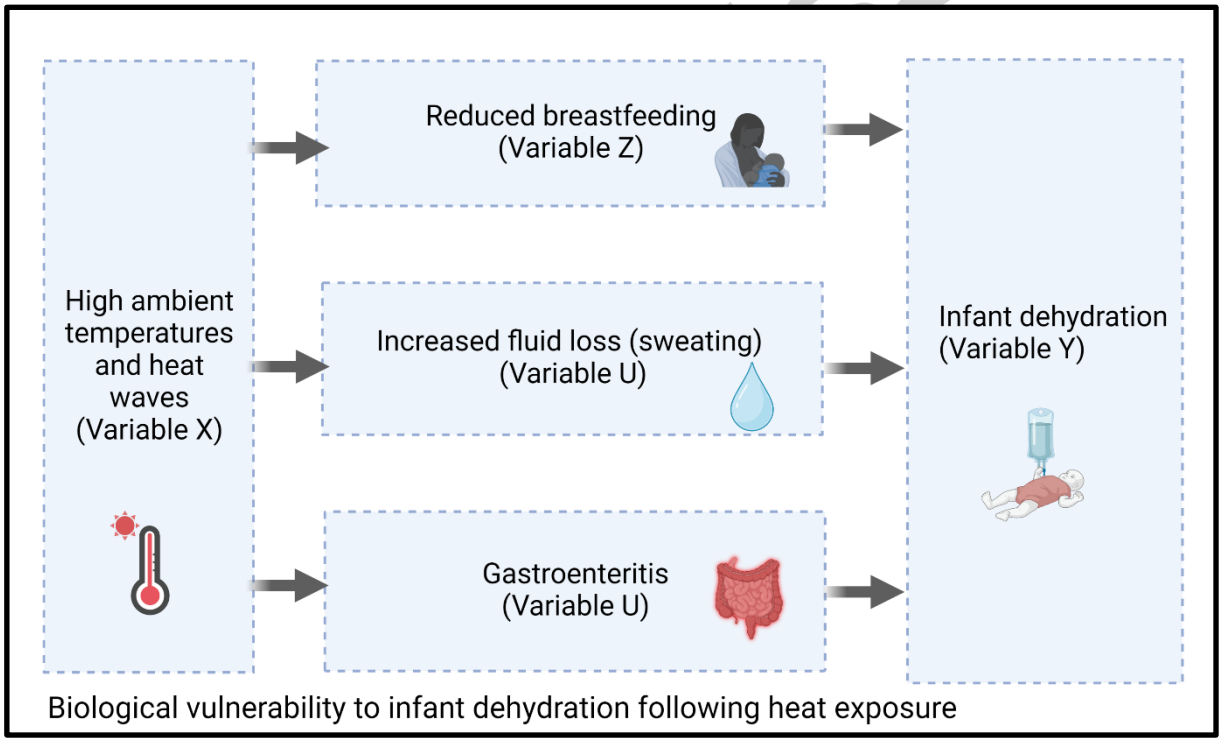
5.2 A systematic review by the Bio-HEAT team located 16 studies demonstrating the adverse impacts of heat among infants[41]. A modelling paper by the group projected that rising temperatures on the continent will cause many thousands of additional child deaths[42]. Chersich and others have proposed a set of physiological, anatomical and social factors that accentuate heat vulnerability in infants, setting out a putative biological pathway[41, 43, 44].

5.3 Exclusive breastfeeding is a central pillar of all initiatives to reduce infant mortality. Breastfeeding

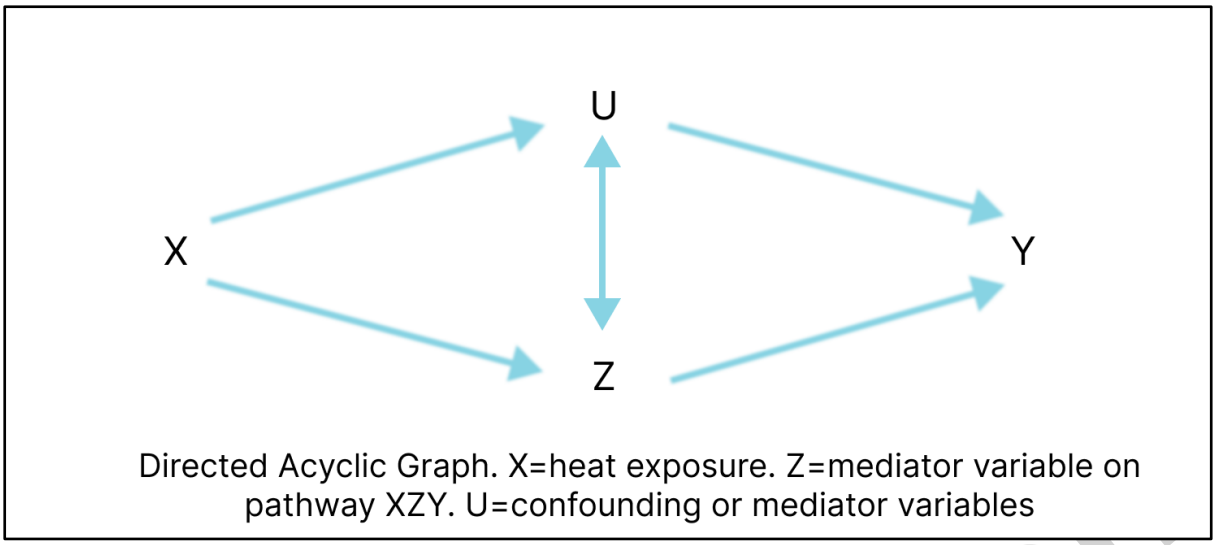
is especially important during hot weather to protect against food- and water-borne infections, which rise in tandem with temperature (see Chersich)[45](Variable U). Ongoing electricity and water outages in the study setting[46] and the hospital itself[47] exponentiate heat impacts on these infections.

5.4 In the CHAMNHA study in Kenya and Burkina Faso, women reported reduced breastfeeding during hot periods as the heat caused considerable discomfort for both them and their infant[48]. This was supported by our quantitative analysis in Burkina Faso, where self-reported breastfeeding duration was about 30 minutes shorter on hotter than on colder days[49]. Concerningly, women may supplement breastmilk with water and other liquids during hot weather, a practice considered harmful[50].

5.5 A systematic review done by several CHAMNHA investigators found that breastfeeding without supplemental water may maintain infant hydration during hot periods[50]. What remains unknown is whether the breastmilk osmolarity changes during hot weather, to compensate for increased fluid loses from sweating in infants and reduced breastmilk intake due to discomfort during breastfeeding. Our third Research Question thus assesses whether breastmilk sodium content declines during hot periods (Variable Z). Self-reported breastfeeding practices among all participants will also be correlated with personal temperature exposure. Additionally, we will use the deuterium oxide dose-to-mother isotope technique[51] to determine whether heat exposure reduces breastmilk volumes (Variable Z). All studies to date on this question have used self-reported data only[50].



Biological vulnerability to infant dehydration following heat exposure



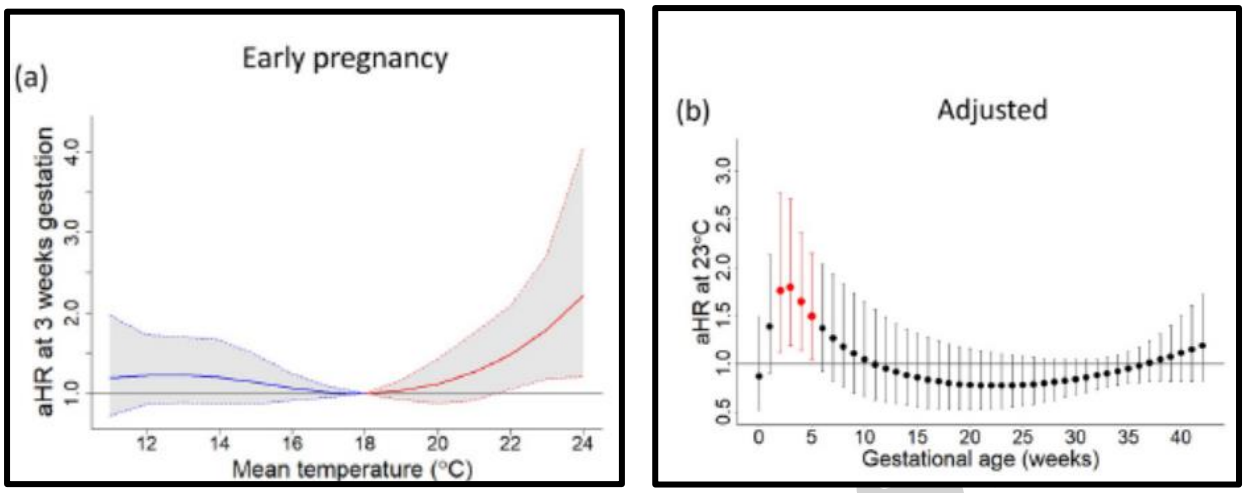
Directed Acyclic Graph. X=heat exposure. Z=mediator variable on pathway XZY. U=confounding or mediator variables

6. Project procedures

6.1 Study sites

6.1.1 The study site, Rahima Moosa Hospital in Johannesburg, South Africa, serves highly-disadvantaged, diverse communities. Within high-density microclimates (''Urban Heat Islands''), temperatures within tin-sheet informal or low-cost houses are often 4-6°C warmer than outdoors (Additional File: Table 1). Few, if any, women in our study population have access to air conditioning, any form of active or passive cooling, or urban greenery. Indoor cooking with fires augments heat exposure.

6.1.2 Globally, people living in areas such as Johannesburg or North European countries, which have traditionally been considered 'temperate', have been shown to be at especially high-risk during heat waves due to limited preparedness and acclimatisation. Adverse birth outcomes can occur even at moderate temperatures in temperate settings[49].



(a) Adjusted hazard ratio (aHR) of PEH (pre-eclampsia, eclampsia/severe pre-eclampsia/imminent eclampsia, or HELLP syndrome) associated with mean weekly temperature 3 weeks. Predictions were centered at 18 ◦C. Red lines indicate temperatures above 18 ◦C and blue lines indicate temperatures below 18 ◦C (50th percentile of daily mean temperature). (b) aHR of PEH at 23 ◦C throughout gestation (95th percentile of daily mean temperature). Red indicates an increased hazard, significant at the 5% level

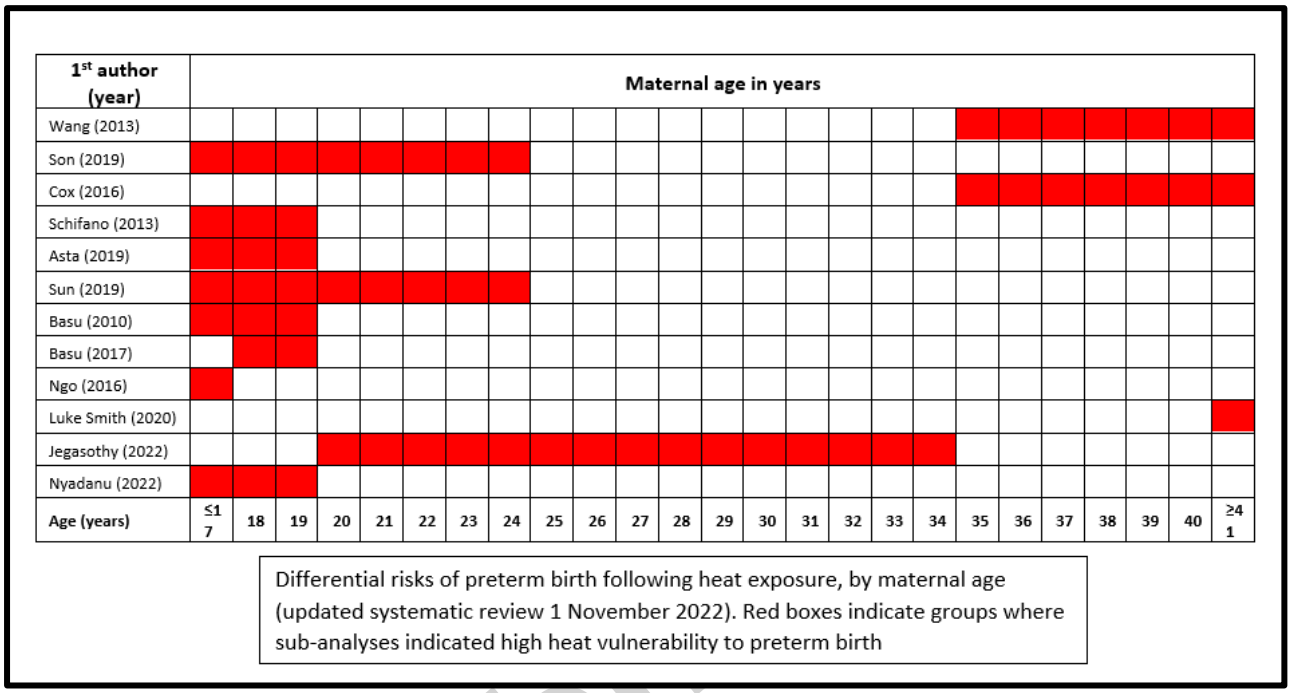
6.2 Preliminary data and synergies with ongoing study activities

6.2.1 The Bio-HEAT study draws on considerable preliminary data, field-tested tools (including for emission measurement). Together with partners, we have a transdisciplinary team of around 30 researchers applying data science techniques to document heat impacts on birth outcomes, including performing causal-pathway analyses using longitudinal data from all countries in Africa[22, 52, 53]. These analyses make use of existing geospatial environmental, sonographic, laboratory and birth outcome data (Additional file: Figure 1). While these analyses provide important data on biological vulnerabilities from heat exposure, the Bio-HEAT dedicated, closely-monitored cohort is an efficient means of filling specific evidence gaps that cannot be addressed using existing data. Moreover, the Bio-HEAT study uses personal temperature exposure data and fine-resolution geolocated data, overcoming major biases in studies using proxy exposure measures.

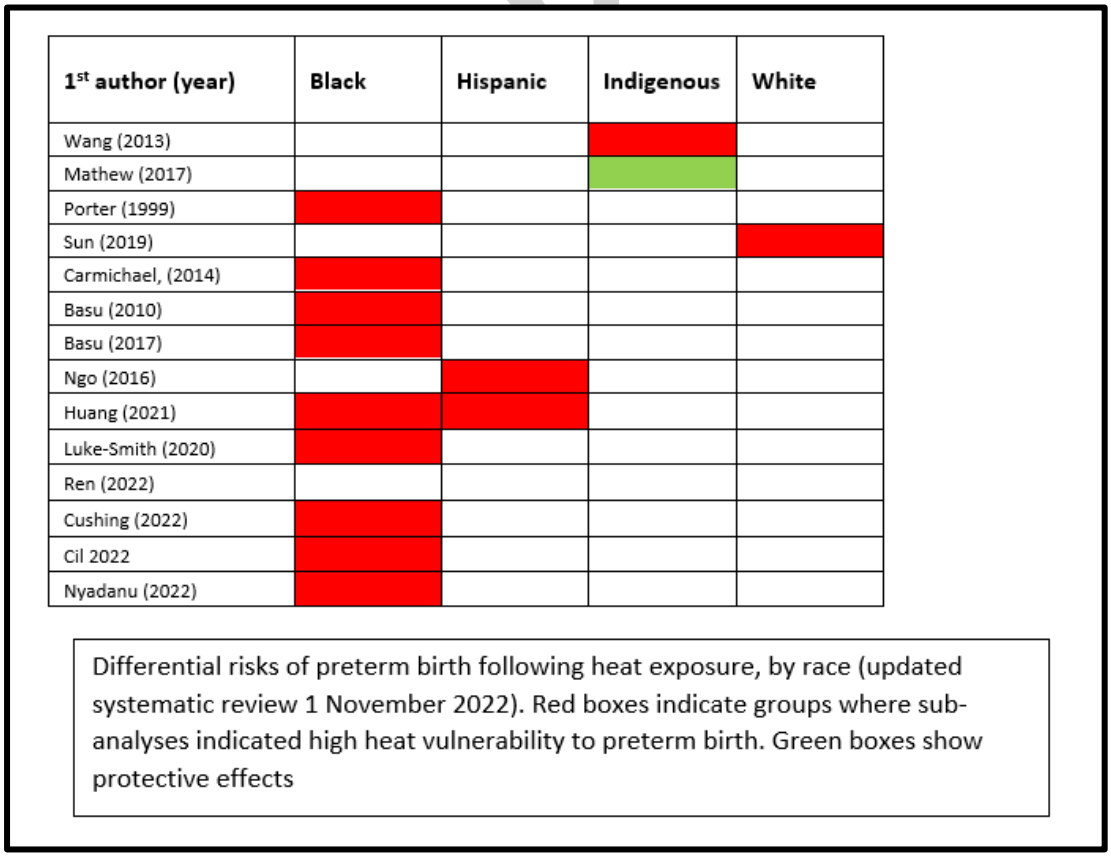
6.2.2 Through the HIGH Horizons project in the study site we are extracting data from birth records over the past 12 months (±15,000 births), and collecting birth-record data prospectively for the next three years[52]. We use these data to describe heat-health associations in the study population and health outcomes such as intrapartum dehydration for comparison with the Bio-HEAT cohort (see Research Question 2). Moreover, our ongoing heat adaptation studies among pregnant women provide a platform for testing protective interventions and bidirectional causality-intervention feedback loops with Bio-HEAT[52, 54].

6.3 Overview of procedures

Over 4-5 months, we will recruit high-risk pregnant women at 12-14 weeks gestation from the antenatal clinic at Rahima Moosa hospital, starting from early spring (the transition season). Risk is defined using evidence from sub-group analyses in our systematic review (see Figure). Women and their infants will be followed until one-year post-delivery. Specific pathways may be explored in more detail or additional tests performed as evidence emerges from the study or related work.



Differential risks of preterm birth following heat exposure, by maternal age (updated systematic review 1 November 2022). Red boxes indicate groups where sub-analyses indicated high heat vulnerability to preterm birth



Differential risks of preterm birth following heat exposure, by race (updated systematic review 1 November 2022). Red boxes indicate groups where sub-analyses indicated high heat vulnerability to preterm birth. Green boxes show protective effects

6.4 Procedures at enrolment

At enrolment, women will self-complete a questionnaire on a tablet, guided by an interviewer, covering socio-demographics, medical and obstetric history, behaviours linked with heat and hydration, access to water and electricity, mental health conditions (depression and post-traumatic stress disorder), and substance use. Women will be assessed for general and central obesity. They will be given wearable 'Fitbits' and instructions on use of the device and the phone app (smart phone coverage is near universal in our population, data costs will be reimbursed).

6.5 Procedures at all scheduled visits

Women will attend scheduled visits at weeks 20, 24, 28, 32, 36 and 40 during pregnancy, and months 1, 3, 6, 9, and 12 postpartum. At each visit, study staff will review the phone app data on heat stress and self-assessed sleep quality, as well as the 'Fitbit' measures of sleep quality, heart rate and activity levels, and collect blood and urine samples. Hydration will be assessed through urea and electrolyte blood testing, and urine osmolarity and specific gravity.

6.6 Procedures during pregnancy

Biophysical sonography will be done at all study visits. Oral glucose tolerance testing and adrenalin and cortisol levels will also be measured at week 28. Using blood samples at weeks 16 and 28. we will perform Luminex assays, covering 26 analytes, including 15 interleukins and TNF-alph, and RNA sequencing. The read-count matrix for differential gene expression and pathway analyses will be produced through the nf-rnaSeqCount pipeline, using the raw RNA-Seq data from the different time points. Heat shock proteins, micro-RNA, and metabolomics will be assessed in funds permit.

6.7 Procedures intrapartum

Continuous foetal monitoring will be done. Water intake will be monitored as described by Hofmeyr[38]. Vaginal swabs will be taken for Group B streptococcus testing.

We will codesign cooling and hydration interventions with health workers, using data from our ongoing adaptation studies. Interventions may include water from water coolers (water outages are common at the hospital[47] and evaporative cooling technologies.

6.8 Procedures postpartum

Participant characteristics measured at baseline will be reassessed at Month 1 postpartum. Women will record the exclusivity, frequency, duration and comfort of breastfeeding on the phone app. Breastmilk samples will be collected and Deuterium oxide dose-to-mother techniques replicating procedures in a similar South African study (n=100)[51].

In infants, data will be collected on anthropometry, gastroenteritis episodes and neurodevelopment. Infant photography at 12 months (frontal and lateral 2D photographs of the face) will be assessed for dysmorphology, especially features of foetal alcohol spectrum disorders. Funding permitting, we will test infant faecal microbiomes which reflect breastfeeding quality and a range of heat effects.

6.9 Procedures during heatwaves

During heatwaves we will conduct home visits to collect additional blood, urine and breastmilk samples, and perform foetal ultrasound using hand-held sonar devices (Quick-Scan). Visits will be done at the time of day with the maximum forecasted daily temperature.

6.10 Procedures at households

Visits to households will confirm house geolocation and building type. We will install indoor and outdoor temperature monitors (n=50 dwellings). Geolocated addresses will be linked with our existing geospatial grid data in Johannesburg within the IBM PAIRS database, including air pollution, noise, ozone and hundreds of other exposure variables (Additional file: Figure 1).

Pre-submission

6.11 Procedures for the nested social science study

Using a phenomenological approach, we will hold serial qualitative in-depth interviews with purposively-selected women. The first interview focuses on understanding their lived experience of heat during the study, and explores psycho-social impacts on heat-health outcomes. At the second interview we will share our conceptual models of the biological and social pathways from heat exposure to adverse maternal and child outcomes. Women will be give feedback on these models and validate them against their own experiences of heat, and resolve key discrepancies or inconsistencies in the model.

6.12 Procedures for measuring heat exposure

All 200 women will use wearable personal temperature monitors as a neck pendant (iButton DS1922) which measures actual air temperature surrounding the woman[55]. Swallowable temperature devices will be used in 50 women during labour. We will thread a temperature probe inside a Foley's Catheter balloon and placed inside the uterus during labour to measure intrauterine temperature, until the foley balloon is expelled, Temperature and humidity will be measured continuously in the maternity ward and in 50 dwellings using digital temperature and humidity sensors on interior walls and adjacent outdoor structures. Long-range wide area network (LoRAWAN) devices will be used. We use Landsat for land surface temperature measures (30m resolution).

6.13 Procedures for Expert meetings or panels

Expert meetings will draw overall conclusions based on all study findings and other published evidence, as done in our previous related projects[8, 56].

7. Project procedures: emission measurement and reduction

Carbon emissions will be quantified using the Aga Khan Health Services Carbon Management Tool[57], which models carbon-producing activities, including the contribution of participant transport, laboratory testing, building energy, refrigerants, consumed grid electricity and supply chains. Overall emissions from the project activities will be tracked six-monthly and minimised where possible.

8. Timetable and milestones

See Gantt chart

Pre-submission

Study procedures and timing of data collection in the Bio-HEAT materno-foetal cohort (n=200 women and infants)

Study procedure	Pregnant women	Intrapartum women	Postpartum women	Infants
Informed consent	Enrolment			
Home visit, address confirmation and housing type	Enrolment. HW		HW	HW
Questionnaire on tablet, or phone app				
Social conditions and economic status	Enrolment		M1	
Access to water, cool spaces and greenery	Enrolment, 4 weekly. HW		M1, 6, 12	
Hydration practices	Enrolment, 4-weekly. HW	Continuous	M1, 3, 6, 9, 12	
Heat-related knowledge and behaviours	Enrolment, 4-weekly. HW		M1, 6, 12	
Heat stress symptoms ('heat diaries')	Enrolment, 4-weekly. HW		M1, 3, 6, 9, 12	
Obstetric and medical history, including co-morbidities, alcohol (AUDIT scale), tobacco and other substance use, medications, especially antiretroviral drugs	Enrolment		M1, 12	
Mental health (Whooley antenatal depression and anxiety, Edinburgh postnatal depression scale, and Primacy Care Post-Traumatic Stress Disorder Screening)	Enrolment		M1, M12	
Breastfeeding exclusivity, frequency, duration and comfort level (WHO 24-hour recall)			M1, 3, 6, 9, 12. HW	
Infant gastroenteritis episodes in infants (2-week DHS point prevalence) and admissions				M1, 3, 6, 9, 12
Pittsburgh Sleep Quality Index, and sleep diary	Enrolment, 4-weekly. HW		M1, 3, 6, 9, 12. HW	
Serial in-depth interviews (n=20-25)	As relevant		M12	
Clinical and ultrasound data				
General and central obesity: body mass index, waist circumference and hip circumference	Enrolment		M1, 3, 6, 9, 12	
Sleep duration and quality ('Fitbit')	Continuous		Continuous	
Activity tracker heart rate and step counter ('Fitbit')	Continuous	Continuous	Continuous	
Labour progress, mode of delivery and maternal morbidity in birth records		Continuous		
Data extracted from patient-held antenatal card, birth record or child health card	Enrolment, 4-weekly	Post-delivery		M1, 3, 6, 9, 12
Foetal ultrasound - 1st trimester screening ultrasound, 2nd trimester anatomy ultrasound, foetal biometry and multi-vessel Doppler studies including uterine arteries, biophysical profile	Enrolment, 4-weekly. HW			
Cardiotocography		Continuous		
Infant anthropometry (weight, length, head circumference)				Birth, M1, 3, 6, 9, 12
Neurodevelopment (milestones, Ages and Stages at M6, Baileys infant assessment M12)				M1, 3, 6, 9, 12
Laboratory procedures				
Inflammatory markers (25-plex luminex panel, including Il-6)	Week 16 and 28 (n=200). HW (n=50)			
RNA Seq gene expression	Week 16 and 28 (n=200). HW (n=50)			
Nutritional status (haemoglobin)	Enrolment		M1	
Maternal hydration and renal function (U&E, urine osmolarity, urine specific gravity)	Enrolment, 4-weekly (urine only). HW	Labour	M1, 3, 6, 9, 12 (urine only). HW	M1, 3, 6, 9, 12 (urine only). HW
Endocrine measures (oral glucose tolerance test, adrenaline, cortisol)	Week 28. HW		HW	HW
Infections (HIV, syphilis, GBS)	Enrolment, 4-weekly (HIV, syphilis)	Labour (GBS)	M1, 3, 6, 9, 12 (HIV)	M1, 3, 6, 9, 12 (HIV)
Breastmilk composition (sodium). N=100 women		Post-delivery	M1, 3, 6, 9, 12. HW	
Breastmilk volume (saliva samples over 14 days, Deuterium oxide dose-to-mother technique), N=100 women			M3	M3
Infant hydration (urine osmolarity, urine specific gravity)				M1, 6, 12. HW
Temperature and environmental exposures				

Pre-submission

Study procedure	Pregnant women	Intrapartum women	Postpartum women	Infants
Personal temperature (wearable device)	Continuous	Continuous	Continuous	
Maternal core temperature (swallowable device; n=50)		Continuous		
Infant core temperature measurement (tympanic)				M1, 3, 6, 9, 12. HW
Indoor household (n=50), maternity facility temperature	Continuous	Continuous	Continuous	Continuous
Outdoors of households (n=50), maternity facility	Continuous	Continuous	Continuous	Continuous
Weather station, satellite remote sensing temperatures	Continuous	Continuous	Continuous	Continuous
Humidity, air pollution, ozone, vegetation, other geospatial data (IBM PAIRS platform)	Continuous	Continuous	Continuous	Continuous

Notes: HIV repeat testing if previous tests are negative. GBS Group-B streptococcus

Pre-submission

	Project years	1												2												3												4					
N	Item Project months	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
	Project Management																																										
1.1	Documentation of reports and financial matters																																									
1.2	Follow up of milestones																																									
1.3	Development of scientific and administrative standard operating procedures																																									
1.4	Development of an Outputs Management Plan																																									
1.5	Monitoring project quality and risk management																																									
1.6	Sign consortium agreement and sub-contracts																																									
1.7	Development of the Steering Committee Terms of Reference																																									
1.8	Formalization of Scientific Advisory Board and Terms of Reference																																									
	Cohort study approvals, enrolment and follow up																																									
2.1	Finalisation of protocol, consent forms and data collection tools																																									
2.2	Ethical and regulatory approvals																																									
2.3	Training of field staff																																									
2.4	Prepare the health facility and communities (community-entry)																																									
2.5	Temperature monitoring in women, households and in the maternity facility																																									
2.6	Enrolment into the cohort study and nested qualitative study																																									
2.7	Follow-up of enrolled participants																																									
2.8	Data management established and maintained																																									
2.9	Data analysis																																									
2.10	Cohort close out																																									
	Expert Group and Scientific Advisory Board																																									
4.1	Meeting of Scientific Advisory Board																																									
4.2	Virtual meetings of Expert Group																																									
4.3	In-person meetings of Expert Group																																									
4.4	Report by Expert Group																																									
	Capacity development, Public engagement and Communication																																									
5.1	Generation of a communication plan																																									
5.2	Capacity building needs assessment and annual review																																									
5.3	Development and review of communication tools and materials																																									
5.4	Community Advisory Board inception and meetings																																									
5.5	Training courses tailored to individual capacity needs																																									
5.6	Online webinars																																									
5.7	MSc and MA research projects																																									
5.8	Doctoral student training and mentoring																																									
5.9	Dissemination of research findings																																									

Gantt chart of study timelines and milestones.

Milestones are shown in boxes with dark red colouring. Some activities will be timed to coincide with periods of hot weather, based on seasonal or sub-seasonal weather forecasting.
Project anticipated start date 1 May 2023

Pre-submission version

Additional information

Pre-submission

List of Additional Figures and Tables

Additional figures

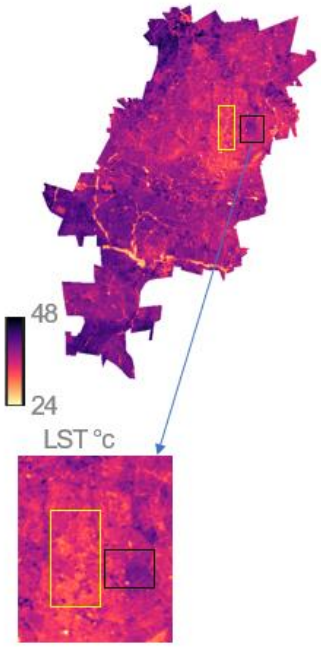
1. Additional Figure 1: Examples of geospatial analyses at fine resolution using the IBM PAIRS platform
2. Additional Figure 5: RNA Sequence analysis

Additional table

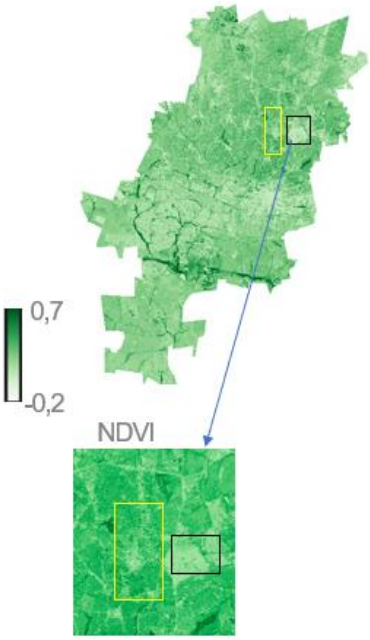
1. Additional Table 1: Climatic and maternal and newborn health characteristics of the study site

Pre-submission

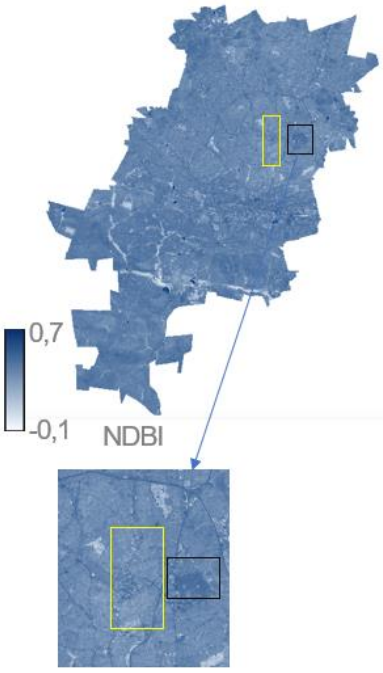
Additional Figure 1: Examples of geospatial analyses at fine resolution using the IBM PAIRS platform



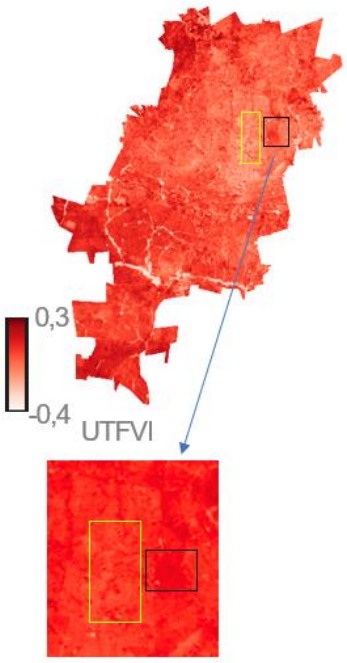
LST: Satellites measure land temperature (LST). LST captures land cover temperature variation based on surface type.



NDVI: measures vegetation using visible (red) and near-infrared light. Higher NDVI means more land. Low NDVI indicates sparse vegetation.



NDBI: Normalization Built-up area Index highlights man-made surfaces and density. Buildings and roads have higher NDBI values. Higher NDBI indicates dense



UTFVI: Uses land surface temperature to measure Urban Heat Island. Higher UTFVI values indicate Urban Heat Island effects.

Sandton is an affluent residential area (yellow box), while Alexandra is an informal township (black box) in Gauteng province of South Africa

Additional Figure 2: RNA Sequence analyses

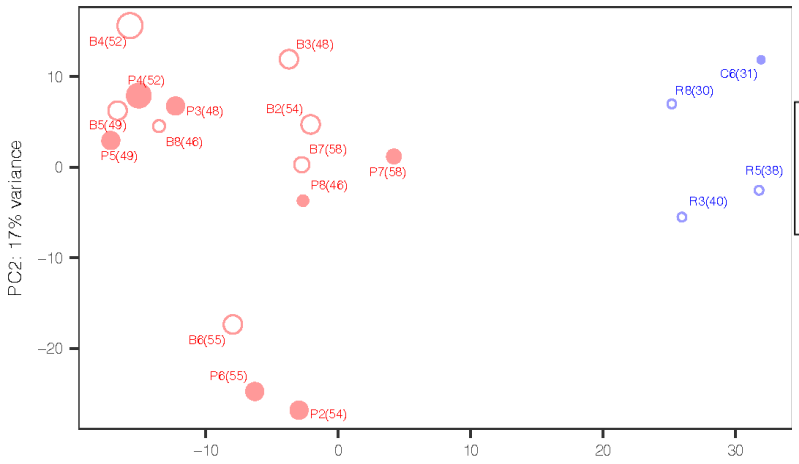


Figure 2a: Principal Component Analysis

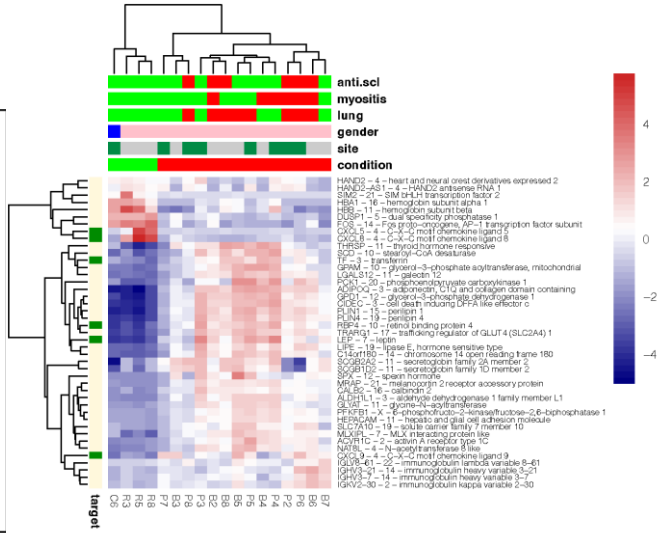


Figure 2b: Heatmaps

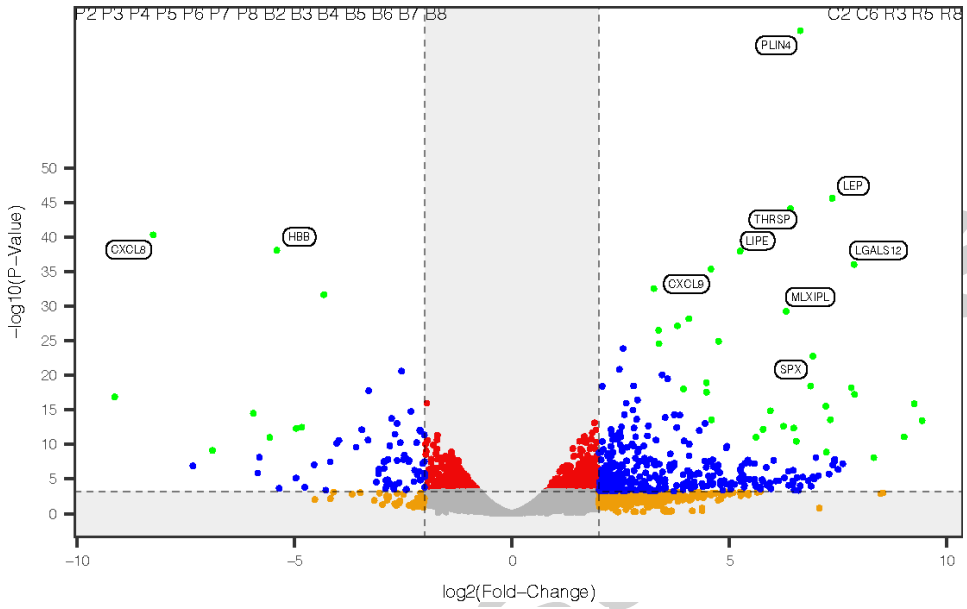


Figure 2c: Volcano plot

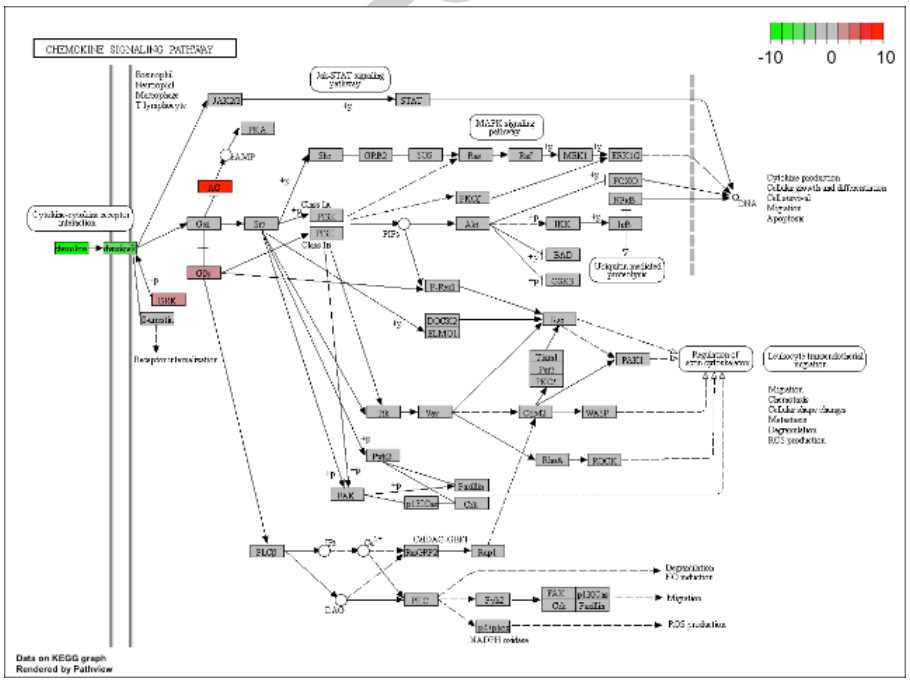


Figure 2d: Pathway graphs

Additional Table 1: Climatic and maternal and newborn health characteristics of the study site

Variable	Rahima Moosa hospital and surrounding areas in Gauteng Province, South Africa
Geographical type	Urban (low-cost housing)
Average daily maximum temperature of the warmest month of the year[1]	28.8°C (January)
The average daily temperature of the warmest month of the year[1]	22.8°C (January)
TMax in October 2022 heatwave[2]	36°C
Days with maximum apparent temperature ≥32 °C (extreme caution needed) between 1979 and 2014[3]	38
Climate zone (Köppen-Geiger classification)[4]	Subtropical climate with dry winters and hot summers
Projected change in temperature 2041-2060 under various mitigation scenarios, relative to 1979-2014[5]	SSP1-1.9: +1.5 °C SSP2-4.5: +1.9 °C SSP5-8.5: 2.3 °C
Projected number of days with maximum apparent temperature ≥32 °C (extreme caution needed) in 2014-2060 under low mitigation[4]	139
Projected change in rainfall [4]	Likely drier
Change in Köppen-Geiger zones over time[4]	Potentially hot steppe under low mitigation futures, as rainfall declines and the hot steppe (drier savannah) expands eastwards (Bsh)
Summary of climate change risks: detected and projected[5]	• Observed and projected decreases in mean precipitation • Observed and projected increases in heavy precipitation and flooding • Observed and projected increase in aridity, agricultural and ecological droughts • Observed increase in meteorological drought, projected increase in meteorological droughts from 1.5°C of global warming, higher confidence at higher global warming levels • Projected increases in heatwave intensities and frequencies • Projected increases in fire weather conditions
Predominant housing type in study population	Informal housing with tin sheeting (47% of women), and low-cost government housing
Deliveries in facility (annual)[6]	15,096
Maternal mortality ratio in facility per 100,000 live births[6]	113
Preterm birth rate in facility[6]	20.7%
Low birth weight rate in facility (<2.5 kg)[6]	19.1%
Stillbirth rate in facility per 1000 live births[6]	22.3
Caesarean section rate in facility[6]	38.4%
Neonatal mortality rate in facility per 1000 live births[6]	16.6
HIV prevalence in pregnant women in facility[6]	19.5%

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IBM South Africa Proprietary Limited
Reg. No. 1952/000308/07
90 Grayston Drive, Sandton 2196
Private Bag X9907 Sandton 2146, South Africa

Telephone: +27 (0) 11 302 9111
Fax: +27 (0) 11 302 9009
http://www.ibm.com/za/

November 10, 2022

Prof. Matthew Chersich
Wits Reproductive Health Institute
University of the Witwatersrand
Hillbrow Health Precinct
22 Esselen Street
Johannesburg
2001
South Africa

Dear Prof. Chersich

I hereby indicate my interest to contribute to the research to be conducted as indicated in your Wellcome Trust application where the aim is to investigate the biological mechanisms informing the adverse maternal health outcomes following from exposure to heat. My contribution to the project will include technical advice on the analysis plan and coordinating the provision of appropriate climate exposure data to support the study, linking heat exposure with immune-inflammatory pathways to preterm birth. I will also contribute to the dissemination of study findings and preparation of manuscripts. This proposed project will build on our existing collaboration with Wits Reproductive Health Institute, under Wits Health Consortium, namely the HEat and HEalth African Transdisciplinary (HE2AT) Center. The HE2AT Center research hub, to which this project will be aligned in terms of leveraging some of the tools and datasets, is focused on developing data science solutions to mitigate the health impacts of climate change in Africa. Therefore, this project will contribute to moving the field forward in understanding the impact of climate on maternal & neonatal health.

Sincerely,

Sibusisiwe Makhanya, PhD
Research Manager
IBM Research Africa
Johannesburg

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Team composition and management
Describe the roles of all applicants and how the project will be managed and led.

Steering Committee. The committee is composed of the lead applicant (Chersich), co-applicants (Gray, Strehlau and Wise) and early-career researcher representatives will provide strategic direction, project management and leadership, project updates, maintain project timelines and review publication 'concepts'. The Committee will be supported by an Operations team that oversees day-to-day operations and administration. The Committee will meet fortnightly, or more frequently, if required. An annual workshop will bring the whole consortium together to review progress and share findings.

Key personnel linkages. The whole project team, aside from Gray, are based at the University of Witwatersrand and interact frequently, which strengthens communication and team cohesion. The work build on long-standing linkages built up through previous research projects which covered clinical, laboratory, field and data science research methods. Over the past 20 years Chersich has collaborated on five projects with the team at Rahima Moosa Hospital, including the ongoing EU HIGH Horizon grant on heat adaptation and maternal health. Mpangase and Chersich are both part of the NIH DS-I data science initiative. Key personnel and other team members are diverse in race, gender and discipline.

Lead applicant Prof. Matthew Chersich takes overall responsibility for coordination, leadership and technical oversight.

Co-applicant Prof. Clive Gray, an immunologist, will oversee laboratory testing and lead the technical aspects of Research Question 1.

Co-applicant Dr Renate Strehlau will be responsible for securing ethics approvals, study implementation and oversight of the cohort, as well as the technical aspects of the post-delivery component (Research Question 3).

Co-applicant Dr Amy Wise will be responsible for study activities in the clinical setting, especially sonography and adaptation interventions in the labour ward (cooling spaces and water supplementation). She will lead the technical aspects concerning foetal medicine, which cut across Research Question 1 and 2.

Collaborators: The team has five collaborators, each experts in key sub-speciality topics relevant to the study.

Dr Phelelani Mpangase will lead bioinformatics analyses of the RNASeq data and give critical guidance on other statistical activities.

Dr Sibusisiwe Makhanya will lead climate science and forecasting activities to guide the timing of study procedures to coincide with heat waves. She will also be responsible for providing geospatial data for the study, drawing on the IBM Geospatial Data Analytics Platform and other spatial datasets from the NIH HE2AT Center.

Prof. Shane Norris, a global expert in epigenetics in pregnancy, as well as foetal development, will lead those technical areas.

Prof. Michael Urban, a clinical geneticist, is responsible for dysmorphology assessment, especially for foetal alcohol spectrum disorder.

Prof. Karl Technau will advise on the design, conduct and analysis of the social science activities.

Dr Gloria Maimela, will secure engagement with the community, provincial and national

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policymakers in South Africa, building on long-standing relationships.

Expert groups. Members will include Prof. Robyn Hetem, a thermal physiologist (Research Question 1), Prof. Justus Hofmeyr, a world leading obstetric researcher (Research Question 2), and Prof. Tanya Doherty, an expert in breastfeeding and Head of the Department of Public Health at Stellenbosch University (Research Question 3).

Select any of the following that apply to your proposed work:
(Proposal involves human participants, Proposal involves the use of human biological material, or identifiable/potentially identifiable data, Neither of the above)

Proposal involves human participants
Proposal involves the use of human biological material, or identifiable/potentially identifiable data

Details of study design for research involving human participants

Describe the study design. This should include, as applicable:

- number of participants in each group;
- how you will allocate participants to study groups;
- type, frequency and duration of interventions and/or health outcome measures;
- details and justification for the power calculation, sample size and proposed statistical analysis. Explain the methods for protecting against bias;
- frequency and duration of planned follow up;
- any other activity with potential significant risks to participants.

Elsewhere in the Application we describe the planned activities, recruitment, inclusion/exclusion criteria, and sequencing of study activities. Risks to participants are expected to be minimal and outlined in the Legal and Ethics section.

1. Cohort study

1.1 Summary

We will implement a single-arm design involving 200 women followed from weeks 12-14 of pregnancy, through to 12 months postpartum (total duration ±17 months). Infants are followed for 12 months. Clinical and laboratory outcomes are measured four-weekly in pregnancy, during labour, and at months 1, 3, 6, 9, and 12 postpartum. Outcomes will be measured through home visits during heat waves.

b. **Overarching principles guiding analyses**

In univariate analysis involving non-clustered data, exposures and outcomes will be compared using Student's t test, Mann-Whitney U test and chi-square test, as applicable. Analysis will account for clustering from repeated measures where relevant, and adjust for seasonal and sub-season patterns to reduce biases from acclimatization or acclimation. Analyses will be presented overall, and by pre-specified population sub-groups (to identify groups for future targeted interventions). We use the Bonferroni correction to counteract potential multiple testing biases.

1.3 Heat exposure measurement

The primary exposure is personal temperature measured through wearable devices. This reduces major differential and non-differential biases in studies using proxy exposure data (e.g., remote sensing or weather stations). Continuous measures of temperature and humidity in dwellings, maternity facility and remote-sensing serve to generate apparent temperature measures and develop predictive models by building type, for example.

Temperature gradients during labour between wearables, swallowables and Foley's catheter thermometers indicate whether women were able to maintain thermoregulation during labour.

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We will model various combinations of apparent temperature, geospatial exposures and outcomes.

1.4 Analysis for Research Question 1

For analyses of biological pathways during pregnancy, the primary study aim, we will associate personal temperatures with interleukin-6 levels (>1000pg/ml, primary outcome). Our omics approach, to enhance precision, includes assessing maternal transcriptomic and epigenetic signatures, using serial RNA-seq, to track up-and down-regulated genes before-and-after heat extremes. Similarities and differences between RNA-Seq samples will be assessed through Principal Component Analysis (Additional Figure 2). To visualise the significantly differentiated genes between the different time points, heatmaps and volcano plots will be created. Pathway analyses of the significantly expressed genes will be carried out using gage and pathview.

1.5 Analysis for Research Question 2

Dehydration, measured through urine specific gravity during labour will be compared with the levels in women delivering prior to the study, matched by population characteristics. Hydration will also be compared through changes in plasma osmolality, intra-individual haematocrits and haemoglobin concentrations and plasma volume.

1.6 Analysis for Research Question 3

We will use paired Student's t tests to determine whether the breastmilk output volumes (measured at five time points) are lower when breastfeeding takes place during the upper quartile of TMax (lag0 days), compared to volumes during the lower quartile. Further analyses will explore linear regression correlations.

1.7 Sample size considerations

Biological pathways analyses involve consideration of a wide range of outcomes. We calculated sample size using binary outcomes as a conservative approach (continuous outcomes will have considerably greater power). The primary inflammatory outcome interleukin-6 (>1000pg/ml) is strongly linked with preterm birth. With 200 women, two measures each and 15% specimen loss, we have >80% power to detect an 8% difference in the primary outcome, assuming that 5% of women exposed to the lowest quartile TMax (lag0_2 days) have raised interleukin-6. A recent study in the Gambia detected Resistance Index changes on sonography with a sample of 40 women. The breastmilk volume study sample size replicates a similar study which was adequately powered.

2. Qualitative research

As part of a mixed-methods approach, qualitative in-depth interviews will be held with purposively sampled pregnant or postpartum women (n=20-25). Interviews will be audio-recorded, translated, transcribed verbatim, and analysed inductively using Grounded Theory.

3. Conceptual frameworks

Drawing all evidence together, will present final biological pathways, with evidence strength for each pathway. All findings will be assessed in week-long expert meetings in Year 2 and 3. Experts will reach decisions through consensus, where possible – defined as the agreement by three quarters or more of the participants. In the absence of consensus, disputes will be put to a vote.

Outline your strategy for recruitment and describe the inclusion/exclusion criteria for study

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participants (if applicable).
If your research includes a clinical trial you must also tell us:

- how you will comply with our policy on ensuring the inclusion of under-served groups and
- how your recruitment and retention methods will engage with under-served groups.

Cohort recruitment strategy

Field staff at antenatal clinics will recruit 2-3 consecutive women per day. Eligibility criteria are:

A. poorest quartile; AND non-white; AND high heat exposure (tin housing, poorly heat-resistant brick housing, or occupational heat exposure); AND ≥1 risk factor for heat-related conditions in pregnancy (<25 years, ≥35 years, gestational diabetes, or obesity).

B. aged ≥16 years

C. week 12-14 of pregnancy (ultrasound ageing)

D. intending to have childbirth in the maternity facility

E. able and willing to give informed consent

Critically-ill women will be excluded from enrolment and from the study activities during periods of acute illness. Infants (from singleton or multiple pregnancies) will be enrolled at birth.

Fifty dwellings will be purposively selected for indoor and outdoor temperature monitoring to reflect different housing types and locales. A swallowable temperature device will be given to 50 randomly-selected women during labour, and all women in labour during heatwaves. Fifty randomly-selected women will participate in breastmilk sampling activities.

Qualitative interview recruitment

Pregnant or postpartum women (n=20-25) will be purposively sampled to include: women with mental health conditions; women who experienced a heatwave during the final weeks of pregnancy; women with preterm birth that was associated with changes in interleukin-6 titres following heat exposure; and women reporting a decline in breastfeeding during hot weather.

Inclusion of under-served groups

We specifically include disadvantaged women, adolescents, and those with co-morbidities. Of note, Wits RHI is a reproductive health and HIV research institute with a long track record in rights-based approaches, initiatives to reduce ‘’unconscious bias’’, and ensuring diversity in study populations. Specific efforts to retain under-served groups will include regular home visits by field staff and fortnightly telephonic contact. The close linkages with the community have enabled the study site to record levels of cohort retention of around 97% over 48-56 weeks follow-up.

How have you involved patients, participants, patient advocacy groups or communities in developing this proposal? What ongoing involvement will they have in the research?

Wits RHI has consulted widely in developing its portfolio of work on heat and maternal and child health. This includes Community Advisory Boards and highly-influential civil society groups, such as the Global Climate and Health Alliance, with whom we hold full membership. We have regular discussions with district and national authorities, who have provided detailed inputs and expressed strong support for our work. We presented our approach to heat research to researcher and policy representatives from 10 African countries at the CHANCE Network meeting in June 2022, hosted by Wits RHI. We conducted a formal Research and Policy Prioritisation Workshop using the CHNRI methods with 54 leading policy makers, researchers, funder representatives, and national and

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international NGOs. The three top-ranked research priority areas on heat and health were: capacity building, health promotion and health services. The top-ranked policy need was “Guidelines on building climate-resilient and environmentally-sustainable health facilities”. Our project addresses each of these top-ranked priorities directly.

As members of the Global Climate and Health Alliance and a key partner of WHO-led Clim-Health Africa, Wits RHI will continue high-level stakeholder involvement throughout the project. Dissemination will take place through scientific publications, conference presentations and meetings, and through our policy networks.

Describe the oversight arrangements for the study. For example, the membership and composition of the Steering Committee, Data Monitoring Board.

Financial and related oversight. WHC will be responsible for the site administrative, financial, human resources and payroll, legal, ethical and regulatory requirements. WHC is committed to adhering to Wellcome Trust’s procedures around financial assurance, and monitoring and auditing of expenditure. Additionally, WHC undertakes sub-recipient monitoring, requiring partners to complete a monitoring checklist at least quarterly, or as per the terms of the contractual agreements. Any unexpected financial, budgetary or conflict concerns will be discussed and resolved by the Steering Committee of the Bio-HEAT study, wherever possible. In instances where the Steering Committee cannot reach consensus, we will seek resolution through discussions with the Scientific Advisory Board of the study, or the Wellcome Trust contact on the project.

Safeguarding. WHC and all partners are committed to safeguarding study participants, staff, students, volunteers, and members of the public with whom we work or interact. We have in place and adhere to a Safeguarding and Security policy, and an anti-bullying and harassment policy, underscored by appropriate oversight mechanisms.

Oversight of study procedures. Dr Renate Strehlau will provide oversight on study participant safety, quality of data, quality of laboratory procedures and cohort retention. Data will be entered into RedCap, with several data quality checks in place. Source documentation will be stored in locked filing cabinets that can only be accessed by the members of the research team who have direct contact with participants. Data quality and range checks are included in data collection tools. Case Report Forms and Source Documentation will be kept in a secure lockable area, accessible only to designated site staff. BARC, the laboratory where most of the laboratory testing will be done, is accredited with the South Africa National Accreditation System in accordance with ISO standards.

Scientific Advisory Board. Anna Coutsoudis (Professor in the Department of Paediatrics and Child Health at the University of KwaZulu Natal, South Africa), a world-leading breastfeeding expert; Collins Iwuji (Professor of Global Health, University of Southampton, United Kingdom) a statistical expert in heat-health analyses; Guido Ferrari (Professor in Molecular Genetics and Microbiology Affiliate, Duke Global Health Institute, Duke University, United States) an immunology and genetics global leader; and Joy Lawn (Professor of Maternal, Reproductive and Child Health at the London School of Hygiene and Tropical Medicine) a world-leader in maternal health have agreed to serve on the Scientific Advisory Board of the project.

The Board is representative in nationality, gender and disciplines. It will meet annually. The Scope of Work for the Board includes: i) making recommendations on advancing the strategic direction of the study; ii) recommending changes to optimise the outputs management and data sharing of the study; iii) critically reviewing project outputs; iv) reviewing, recommending and facilitating links with external organisations, strategic partnerships and networks to increase the activity and impact of the study; and v) facilitating links with super-specialist experts in specific content areas, tailored to emerging study findings.

Community oversight. Community leadership and ownership is a key determinant of the success of the study, and is essential for safeguarding participants and for ensuring high rates of retention of

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participants in the cohort. The insights of the community help ensure that the outputs we generate and disseminate are relevant and responsive to the needs of local communities and stakeholders. Community oversight is particularly critical given escalating levels of concern about climate change, and the concomitant demand for actionable information on the topic. Equally, community involvement is important for dispelling harmful misconceptions or denialism around climate change.

Community Advisory Boards. The Board will meet quarterly, providing oversight of study activities and ensuring the voices of the community are represented throughout and beyond the study period. The Board will also provide critical inputs on the planning and implementation of research activities to ensure that our activities align with local needs and are culturally appropriate.

Who has, or will, review the ethics of the project and when? Detail any other regulatory approvals you have obtained, or will seek.
We reserve the right to see relevant approval documents at any point during the grant and after it has ended. This is in accordance with our research involving human participants policy.

Legal and ethical guidelines

The project will ensure the protection of the rights, interests and safety of human participants and their data through procedures that adhere to the following legal and ethical guidelines:

International:

1. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects (General Assembly of World Medical Association 2014)

2. International Council for Harmonisation (ICH) Good Clinical Practice E6(R2)

3. Nuremberg Code (1947)

4. Council for International Organisations of Medical Sciences (CIOMS) guidelines (1949 to present)

South Africa:

1. Department of Health. Ethics in Health Research - Principles, Processes and Structures, 2nd edition (National Health Research Ethics Council 2015)

2. Protection of Personal Information Act (2021)

3. National Health Act (2003)

Local ethical and regulatory bodies

The study protocol, participant informed consent and information sheet, study staff documentation, and other supporting documents will be submitted for review by the Wits Human Research Ethics Committee (Wits HREC). In addition, approval for the study will be sought from the Gauteng Provincial Department of Health. The study will be registered on the South African National Health Research Database.

The Lead Applicant assumes responsibility for ensuring that all appropriate ethical, regulatory and facility approvals have been secured prior to commencing the study, and that ongoing procedures adhere to the study protocol. The study will have safeguards in place to ensure that risks, abuse and the harassment of participants are prevented. We will provide regular updates to Wellcome Trust on the status of our applications in the approval processes and share all the relevant approval documents with the Trust as these become available.

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Below, we detail how we will comply with the above-mentioned legal and ethical guidelines: Firstly, in ethics applications, we will highlight potential ethical concerns regarding the research, including potential risks to participants and how these will be limited. We will detail the process of obtaining informed consent or assent, and how participants will be protected from harm during the research. Should any amendments to study activities be required, these will not be implemented prior to the receipt of the required approval(s), except where necessary to eliminate apparent immediate hazards to study participants. The ethics committees will be updated yearly on the study progress, if a serious adverse event occurs, or as required by the Ethics Committee.

Secondly, we will ensure that all staff undergo appropriate ethics training that meets the in-country or Ethics Committee requirements, as well as the necessary protocol training, and required qualifications prior to conducting study procedures.

Thirdly, we will closely monitor the safety of participants, inform them of any adverse findings, and refer to and ensure that participants can access optimal local standard of care, if required. We anticipate minimal risk to participants associated with the intervention and participation in the study. The main potential drawbacks of study participation will be opportunity costs for women and potentially augmented stress for those who have experienced complicated childbirth or adverse perinatal events. Insurance cover for compensation will be procured for study participants in the unlikely event of any injuries or damage caused by taking part in the research.

We are aware that women in South Africa who wear an activity or sleep tracker on their wrist may be potential targets for criminals. We will consult with pregnant women and our Community Advisory Boards about these risks and exclude these devices from the study if there are substantive concerns. Staff will protect participant confidentiality through the use of participant identification numbers instead of participants' names and limiting access to participant's data. Any samples collected from participants during the study will be processed within South Africa. All data collected from participants including transcripts, fieldnotes and biomedical data will be stored in a secure server with access only granted to project staff directly involved in the study. Data shared on public access platforms will be de-identified and adhere to the Wellcome Trust's policies for data accessibility and sharing. Interviews will be audio-recorded and transcribed in full, with all identifying information removed from the transcripts, apart from gender, age, population group and facility name. Audio-recordings and transcripts will be stored in a secure folder and saved to the Amazon Web Services cloud-based computing platform with password-restricted access limited to the investigators and other study staff, and stored separately from other participant records, such as informed consent forms that may identify individuals. After the study has been concluded, audio recordings will be destroyed in accordance with the time specifications mandated by South African research ethics guidelines, and the Wellcome Trust guidelines, as relevant. All the processes described above will be outlined in a detailed data management plan.

Will you be using facilities, staff or patients within the National Health Service (NHS) in the UK?	No

Which organisation(s) has/have agreed to act as the formal sponsor(s) for your project?
The Wits Health Consortium (WHC), a wholly-owned subsidiary of the Faculty of Health Sciences, University of the Witwatersrand is the formal sponsor of the Bio-HEAT project. The Consortium complies with regulations relating to research with human participants as prescribed in the National Health Act (2003). The Act led to the establishment of the National Health Research Ethics Council (NHREC), a statutory body that determines guidelines for the functioning of Ethics Committees, such as that administered by the University of the Witwatersrand. The Wits Health Consortium fully understands the responsibilities and costs associated with being an organisation sponsor.

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Confirm you have in place, or you will seek, appropriate informed consent to use any potentially commercially exploitable results from tissues or samples derived from human participants. Where data has the potential to be used beyond its initial purpose or beyond the end of the study, include details for how the consent will be managed.
Prof. Matthew Chersich, the Lead Applicant, confirms that the Bio-HEAT study team will seek appropriate informed consent from study participants for the use of any potentially commercially exploitable results from tissues or samples derived from human participants. From the onset of the study, we will consider appropriate future uses for the study data and will design the consent processes to accommodate this, as per the Wellcome Trust guidelines. We will have a separate informed consent form that requests use of the participants' anonymised study samples and data for (re-)analysis in studies done for purposes other than this study, and beyond the end of the study. If participants do not agree for their data to be used in other studies, they will still be permitted to join the study. If the opportunity to use the data in a way that was not anticipated arises while the study is still in progress (or if feasible thereafter), we will consider reconsenting participants and updating the information on transparency available to them.

Does your proposal involve a clinical trial?	No

5. Outputs management and sharing

Provide an outputs management plan All Wellcome-funded researchers are expected to manage their research outputs in a way that will achieve the greatest health benefit, maximising the availability of research data, software and materials with as few restrictions as possible. Our guidance on developing an outputs management plan, which includes a link to some good examples, is available here. If an outputs management plan is not required, please briefly explain why below.
What outputs will this research generate? 1. Individual participant data gathered through repeated measurement of clinical, radiological and laboratory outcomes, and qualitative enquiry. 2. Research outputs such as publications, expert group meeting reports, and conference presentations 3. Progressively-refined causal frameworks depicting biological vulnerability to heat exposure, with assessments of strength of evidence for each step of the pathway 4. Concepts for future research on protective interventions against heat exposure during pregnancy, intrapartum, and postpartum 5. Social and traditional media engagements, building on existing links with the National Geographic, New York Times, eNCA television among others. **What metadata and documentation will accompany outputs?** Metadata include data dictionaries and data descriptors such as names of Principal Investigators, funding sources, protocols, generic informed consent form, Standard Operating Procedures (SOPs), sample types and sampling procedures, temporal and geographic coverage of data, look-up tables, technical information (e.g., file formats), interviewer guides, coding instruments, and other suitable metadata identified during the project. **When will outputs be made available?** Individual participant data will be shared immediately upon publication, with a data sharing statement that provides guidance on data access. We will consider sharing data pre-publication through a publication moratoria.

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Where will outputs be made available? The study will be registered on suitable platforms such as the National Health Research Database in South Africa and ClinicalTrials.gov, and the study protocol made available where possible. Metadata, data and code generated will be saved in data repositories, such as Github, Figshare Vivli, or Zonodo.

How will outputs be discovered and accessed? We use DataCite which automatically assigns Digital Object Identifiers, enhancing output linking, citation and tracking. We will develop data-access SOPs for responsible access granting mechanisms and publicise these on the Wellcome Open Research platform. Open database licences, such as Creative Commons and the Open Source Initiative will promote data access. Outputs will be accessed at conferences, community and policy-maker meetings, and through press statements.

Possible restrictions and data storage considerations. Individual participant data will only be shared if participants have agreed to data sharing in the study informed consent form. Additional restrictions will be guided by national legislation (POPIA Act in South Africa and any other country-specific data protection legislature if data is moving across borders). Data will be stored on a secure cloud-server and participant-identifiers stored separately, linked through Unique Participant Identifiers. Only deidentified data will be shared.

Dedicated resources. We will not require any additional resources for outputs sharing. WHC, the legal custodian of project outputs, and the broader Wits University, have data management services to ensure secure data storage, and that platforms are interoperable and maintained beyond the study. Chersich is the data management custodian.

Intellectual-property (IP) outputs. We will adhere to Wellcome Trust's guidelines on IP that has the potential for patenting and commercialisation. To protect Wellcome Trust-funded IP, WHC will be IP custodian, with binding contracts to protect IP outside the study consortium, as per Wellcome Trust policies. Alf Farell, Chief Executive Officer (afarell@witshealth.co.za) is the point-of-contact for protection and commercialisation of IP.

6. Collaborations

Are any collaborations essential for this proposal? This could be through sharing facilities, providing access to resources (essential reagents, samples, data) or sharing subject-specific knowledge and guidance.	Yes

List any key collaborators (name and organisation) and provide a very brief outline of their role in the proposed research.

Name	Organisation	Outline of role in proposed research (50 words max)
Dr Phelelani Mpangase	Sydney Brenner Institute for Molecular Bioscience, University of the Witwatersrand, South Africa	Dr Mpangase (BSc (Hons), MSc, PhD) is a leading bioinformaticist responsible for analysis of the RNA Seq reads, including quality assessment, and differential expression analysis. Most importantly, he will do pathway analyses of the significantly expressed genes and develop pathways graphs, linking these to

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List any key collaborators (name and organisation) and provide a very brief outline of their role in the proposed research.		
Name	**Organisation**	**Outline of role in proposed research (50 words max)**
		heat exposure. ORCID: 0000-0001-8280-8940.
Prof. Michael Urban	Division of Human Genetics, University of the Witwatersrand, South Africa	Prof. Urban (MBBCh, FCPaed, subspeciality (Medical Genetics), PhD) is a highly-experienced clinical geneticist who will perform dysmorphology assessments using infant photographs and specifically review the photos for evidence of foetal alcohol spectrum disorders. He has collaborated with Chersich for 20 years and brings important epidemiology and management skills. ORCID: 0000-0002-9392-0206
Dr. Sibusisiwe Makhanya	IBM Research Africa	Dr Makhanya, (BSc(Hons), MSc, PhD Spatial Statistics), a Research Scientist and Manager, will contribute to statistical learning and modelling, including spatial statistics and quantitative risk assessment around climate extremes and air quality. She has rich experience with risk assessment, high-resolution population mapping, and methods for prioritising adaptation interventions. ORCID: 0000-0001-6481-2356
Prof. Shane Norris	University of Southampton, United Kingdom and University of the Witwatersrand, South Africa	Prof. Norris (PhD) a global expert in epigenetics in pregnancy, life-course epidemiology, inter-generational impacts, as well as foetal development, and will lead those technical areas in the Bio-HEAT study. His other inputs include nutrition and body composition, longitudinal-cohort study methodologies and interventions to improve maternal and child health. ORCID: 0000-0001-7124-3788
Prof. Karl Technau	Empilweni clinic, University of the Witwatersrand, South Africa	Prof. Technau (MBBCh, PhD) will lead the design, conduct and analysis of the social science activities, drawing on his rich experience of interactions and

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List any key collaborators (name and organisation) and provide a very brief outline of their role in the proposed research.		
Name	**Organisation**	**Outline of role in proposed research (50 words max)**
		research studies with patients and study participants around the impacts of mental health conditions and psycho-social circumstances, especially during pregnancy and postpartum. ORCID: 0000-0001-7367-7512

I confirm that the collaborators named above have agreed to be involved, as described, in the proposed research and are willing for their details to be included as part of this application.
Confirmed

7. Location of activity

Will the funded activity take place at more than one location? List any locations outside of your host organisation where you will be conducting research or redirecting funds. This includes, but is not limited to, anywhere in receipt of indirect funding, Wellcome Trust supported facilities, fieldwork sites, and time spent working in another organisation/laboratory. This does not include conference attendance.	No

Will the project be based in one of the following Wellcome Trust supported facilities: • the Wellcome Trust Sanger Institute • a Wellcome Trust Centre • an Africa and Asia Programme • the Francis Crick Institute? If the project will be based at one of these facilities, add the facility as a location above.	No

Will you require funds to be awarded directly to more than one location? We will only consider requests for funds to be awarded directly to more than one location if: • your award includes a request for multiple currencies. Any request for additional currencies must be at least the equivalent of £750,000; and/or • your award involves an organisation based in a low- or middle-income country. We will assess the financial capacity of the organisation to manage the award. If we award directly to more than one location, we will not move funds between organisations after we have issued the award letter.	No

8. Research involving animals

Select any of the following that apply to your proposed work: *(Proposal involves the use of animals, Proposal involves the use of animal tissue, Neither of the above)*
Neither of the above

9. Risks of research misuse

Confirm that you have considered whether your proposed research could generate outcomes that could be misused for harmful purposes.
Confirmed

Have you identified any tangible risks of this type?	No

10. Freedom to operate/conflicts of interest

Describe any freedom to operate or other intellectual property related issues that might affect your ability to carry out the proposed research and/or to use, share or commercialise the research outputs. Explain how you will address these.

If you are satisfied that there are no such issues, enter N/A. If you have fully addressed such issues in your outputs management plan under the question on "Outputs management and sharing", then you may refer to that answer.

In particular, consider the following:

- Will your research use technology, software, databases, materials or patented inventions that are owned or controlled by others and which you do **not** already have written permission to use?
- Will the ownership, use, commercialisation and/or sharing of research outputs with the wider research community, be subject to agreements with commercial, academic or other organisations? This includes arrangements with collaborators named in this application.

N/A

Describe any conflicts of interest which might affect your ability to carry out the proposed research and/or to share or commercialise the research outputs.
For each conflict:

- explain how you and your organisation will manage the conflict
- explain how you will comply with your organisation's requirements in relation to conflicts of interest
- confirm whether the identified conflict has been disclosed to your organisation.

If you are satisfied there are no issues, enter N/A.

Refer to our policy on conflicts of interest related to Wellcome-funded researchers and commercial organisations. In particular, consider whether anyone involved in your project holds any consultancies, advisory roles, or equities in, or directorships of, companies or other organisations that might have an interest in the results of your proposed research.
N/A

11. Lead applicant details

Lead applicant details	
Full Name	Prof Matthew Chersich
Department	Wits Reproductive Health and HIV Institute
Organisation	University of the Witwatersrand

ORCID iD	
ORCID iD	0000-0002-4320-9168

Career history (current/most recent first)

From	To	Position	Organisation
01/2018	01/2042	Research Professor	Wits RHI, Faculty of Health Sciences, University of the Witwatersrand, South Africa
07/2014	12/2017	Associate Professor	Wits RHI, Faculty of Health Sciences, University of the Witwatersrand, South Africa
01/2011	06/2014	Associate Professor	School of Public Health, Faculty of Health Sciences, University of the Witwatersrand
01/2009	05/2022	Visiting Professor	Faculty of Medicine and Health Sciences, Ghent University, Belgium
01/2007	12/2010	Technical Advisor	Reproductive Health and HIV Research Unit, University of the Witwatersrand, South Africa
01/2005	12/2009	Epidemiologist and Statistician	International Centre for Reproductive Health, Mombasa, Kenya
01/2004	12/2004	Technical Officer	World Health Organization, Geneva, Switzerland
08/2003	12/2003	Consultant	World Health Organization, Geneva, Switzerland
06/2002	12/2003	Locum Senior Medical Officer	National Health Service, United

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Career history (current/most recent first)			
From	**To**	**Position**	**Organisation**
			Kingdom
01/2001	06/2002	Trial Physician	Perinatal HIV Research Unit, University of the Witwatersrand, South Africa
01/2000	12/2000	Community Service Medical Officer	Coronation Mother and Child Hospital, Johannesburg, South Africa
01/1999	12/1999	Medical Intern Doctor	King Edward III Hospital, Durban, South Africa

Education/training				
From	**To**	**Qualification**	**Subject**	**Organisation**
01/2007	11/2007	Diploma Faculty of Public Health	Public Health	UK Faculty of Public Health
01/2006	12/2007	Doctor of Philosophy (PhD;DPhil)	Medicine & Health Science	Ghent University
09/2002	08/2003	Master of Science (MSc)	Public Health in Developing Countries	London School of Hygiene & Tropical Medicine
01/2002	11/2002	Diploma in Tropical Medicine and Hygiene	Infectious diseases	University of the Witwatersrand
07/2000	03/2001	Diploma in Child Health	Paediatrics	College of Medicine, South Africa
01/2000	09/2000	Diploma in Obstetrics	Obstetrics	College of Medicine, South Africa
01/1993	12/1998	Primary Med Qual (BM;MBChB;MBBS;MD)	Medicine and Surgery	University of the Witwatersrand

Career breaks Have you taken any breaks from research that you wish us to take into consideration? This can include periods of parental or long-term sick leave, caring responsibilities, part-time work, secondments, volunteering or time spent in different sectors. You can also include any periods where you were unable to work because of the COVID-19 pandemic.	No

Do you wish to undertake this award part time? If you wish to undertake this award part-time, either from the start or part way through the grant, your host organisation must employ you on a part-time basis during that time.	No

Source(s) of personal salary support State all your sources of salary funding (for example, through your organisation's block grant from a higher education funding body), and the percentage of your salary they contribute. Answer 'not applicable' if you are not currently employed.
US NIH (HEat and HEalth African Transdisciplinary Center: HEAT Center) 75%. European Union Horizons (HIGH Horizons) 5%. European Union Horizons (ENBEL project) 15%. Belmont Forum (Climate, Heat and Maternal and and Neonatal Health in Africa: CHAMNHA project) 5%.

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Are you a healthcare professional? This information is used to understand salary requests (where eligible), research time commitments and to report on our funding.	Yes

Indicate your healthcare profession
Non-medical Public Health Specialty Trainee, specialist or Consultant

Are you clinically active?	No

What is your specialty? If your specialty is not on the list, select 'Other' and specify.
Other

Specify
Climate Change and Health

Career contributions
In relation to this application, summarise what you consider to be your key experience and achievements/contributions (e.g. publications, patents, impacts on policy). For each, provide details of when it came about, why you think it is important and what impact it has had.

Since 2020, I have conceived and secured four large, highly-competitive international grants on climate change and health, including two NIH-funded grants and two European Union Horizons grants. These projects, which are pioneering in climate change research, involve more than 30 partners and four field sites in Africa, and have already made significant contributions to evidence. Additionally, I conceptualised the CHANCE network, which brings together key policy and research partners in Africa, and have raised funding for five years of network activities. These activities led to the establishment of a Directorate on Climate and Health at Wits RHI, a major step change for climate change research at my University and in Africa.
I was a leading contributor to the South African Heat Adaptation guidelines and a contributing author on the Africa chapter of the 6th IPCC report. I also serve on the WHO Climate Change and Health Civil Society Working Group. I have contributed to 14 WHO guidelines or monologues, including as a guideline writer, lead on systematic reviews or methodology, or technical expert. My publications on climate change (17 in 2022) include two commentaries and an expert meeting report on biological vulnerability to heat exposure in pregnancy. My interventional research on heat adaptation in pregnancy (CHAMNHA, HEAT Center and HIGH Horizons) provides a foundation for testing protective interventions identified in Bio-HEAT, but also provides insights on causal mechanisms. My academic career over 20 years includes participation in 80 studies, more than 200 journal articles or book chapters, an H-Index of 54 and over 10,500 citations. I have worked closely with most investigators in Bio-HEAT, including over 20 years with the research site. Currently, I am guest editor on a special edition on Climate Change and Health in the journal Health Policy and Planning. Finally, I am leading the fossil fuel divestment movement at my University, a role that leverages my membership of the University Senate, and all my recent studies include measuring emissions and minimisation. Taken together, my work on climate change and health is increasingly playing an important role in shaping the research and policy agenda in the field.

Positive and inclusive working/research culture
Describe your approach to developing and supporting a positive and inclusive working/research culture, including examples from previous and current groups. This could include, for example:

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- mentoring
- supporting collaboration and interdisciplinarity
- leadership and people management
- promoting research integrity.

My approach to leadership and people management centres on holding frequent open discussions around work processes and outputs, underscored by strong interpersonal relations and regular check-ins around wellbeing. Additionally, I place much emphasis on maintaining collegial relations and collaborations with peers, investing considerable time in building engaging and productive relations.

I am acutely aware that problem solving and finding solutions in our research context requires a positive research culture, and an inclusive and engaged research team that integrates diverse groups of people, types of knowledge, data, and understandings. All my current research projects on climate change and health involve transdisciplinary groups, encompassing thermal physiologists, biomedical and climate science experts, public health practitioners, social-behavioural scientists, as well as data scientists. The Bio-HEAT project, which was built on these firm foundations, draws seamlessly from several sectors and disciplines, and provides a testament to my ability to successfully establish and capitalise on synergies across disciplines, while navigating the potential challenges of this approach.

Overall, my mentoring activities have centred on supporting early-career researchers to produce high-quality research articles, shepherding researchers through each stage of this process, with much success. A large cohort of researchers wrote their first journal article under my mentorship, with that experience playing a major role in generating enthusiasm for scientific writing. One approach I have successfully employed to build a positive research culture has been to set up a journal special edition involving a group of early- and mid-career researchers. Members of the group then interact frequently, especially during dedicated writing retreats. Three such journal series under my leadership have been completed to date, and a fourth is underway. Teaching and student supervision are not a major focus in my position at Wits RHI. However, over the past eight years, I have supervised four doctoral and four master's students to completion of their studies.

Since its inception 25 years ago, Wits RHI's key focus has been on health of disadvantaged women. Ensuring safe and positive spaces for women in research is deeply ingrained within the Institute's culture and underpins all relations in my team. My own efforts to promote inclusive, diverse and representative research teams havehelped to create a tolerant, non-discriminatory research environment conducive to developing early-career researchers. Transformation along race and gender lines to achieve greater diversity in scientific leadership has been central to my work, and I view this as essential for developing an inclusive working culture given the particular historical racial discriminations in South Africa. Efforts include specifically aiming to recruit and train researchers from historically-disadvantaged groups, especially Black African and female early-career researchers. I acknowledge the imperative to redress historic inequalities in access to employment, and include this as a criterion during staff recruitment and in activities such as conference panels. These principles have been successfully actualised in the Directorate of Climate and Health at Wits RHI. Of eight researchers, six are female, and five are black. Based on the above foundations, together with others, I have developed a highly-productive, diverse and happy work environment.

Current and recent funding (including Wellcome grants)
List any funding you have received in the last five years, including current funding.

List the most recent first. State the name of the funder, name(s) of grantholder(s), title of the project, total amount awarded (and how much of this you received), your role in the project, and the start and end dates. State the percentage of your time spent on the research.

The Wits RHI is wholly grant funded and does not receive any core funding from the University.

Title of the project: Heat Indicators for Global Health (HIGH Horizons): monitoring, Early Warning

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Systems and health facility interventions for pregnant and postpartum women, infants and health workers.
Name of funder: European Union, Horizon programme
Name of grant holder: University of Ghent, Belgium
Total amount awarded: €10,000,000
Total amount received by Wits RHI: €2,500,000
Role in the project: Co-applicant
Start and end date: 09/2022 to 08/2026
Percentage of time currently spent on the research: 5%
Role in obtaining the funding: Lead grant writer on technical sections of the proposal

Title of the project: The HEat and HEalth African Transdisciplinary Center (HE2AT Center): Developing data science solutions to mitigate the health impacts of climate change in Africa
Name of funder: United States National Institutes of Health (U54 grant mechanism)
Name of grant holder: Wits RHI, University of the Witwatersrand, South Africa
Total amount awarded: $6,500,000
Total amount received by Wits RHI: $2,655,000
Role in the project: Overall Principal Investigator
Start and end date: 09/2021 to 08/2026
Percentage of time currently spent on the research: 75%
Role in obtaining the funding: Lead applicant and lead grant writer

Title of the project: ENhancing BELmont Research Action to support EU policy making on climate change and health (the ENBEL project)
Name of funder: European Union, Horizon programme
Name of grant holder: Center for International Climate Research (CICERO), Norway
Total amount awarded: €3,000,000
Total amount received by Wits RHI: €285,000
Role in the project: Co-applicant
Start and end date: 09/2020 to 12/2023
Percentage of time currently spent on the research: 15%
Role in obtaining the funding: Lead grant writer on the technical component of the proposal

Title of the project: Climate, Heat and Maternal and Neonatal Health in Africa (the CHAMNHA project)
Name of funder: Belmont Forum funded by the Natural Environment Research Council (NERC), Research Council of Norway (RCN), the Swedish Research Council for Health, Working Life and Welfare, the Swedish Research Council (Forte), CRN, Norway, US National Institutes for Health
Name of grant holder: London School of Hygiene and Tropical Medicine, United Kingdom
Total amount awarded: €1,900,000
Total amount received by Wits RHI: €160,000
Role in the project: Joint Lead Applicant
Start and end date: 01/2020 to 12/2023
Percentage of time currently spent on the research: 5%
Role in obtaining the funding: Lead grant writer

Title of the project: Trans-disciplinary research to more effectively manage the impact of increasing ambient temperatures on health outcomes in Kenya
Name of funder: Global Innovation Fund (University of Washington, USA, and Aga Khan University, Kenya)
Name of grant holder: University of Washington
Total amount awarded: $38,000
Total amount received by Wits RHI: $0
Role in the project: Investigator
Start and end date: 07/2020 to 06/2021
Percentage of time currently spent on the research: 0% at present

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Role in obtaining the funding: Consortium member

Title of the project: Determining the epidemiological parameters of COVID-19 through serosurveillance with Dried Plasma Spots and nested household transmission studies in rural Kenya and South Africa (the COREP project)
Name of funder: European and Developing Countries Clinical Trials Partnership (EDCTP)
Name of grant holder: University of Heidelberg, Germany
Total amount awarded: €500,000
Total amount received by Wits RHI: €40,000
Role in the project: Investigator
Start and end date: 05/2020 to 06/2022
Percentage of time currently spent on the research: 0% at present
Role in obtaining the funding: Lead grant writer

Describe how the currently active grants listed above relate to this application. If you hold grants related to the topic of this application, explain how these differ and confirm there is no overlap in funding.
Bio-HEAT is highly complementary to the above grants. Specifically, Bio-HEAT activities have already and will continue to be shaped by findings from the CHAMNHA, HEAT Center and HIGH Horizons projects, which re-analyse longitudinal data on maternal and child health to document heat impacts and causal mechanisms. These studies include some haematological and renal function tests, helping to delineate pathways relevant to Bio-HEAT. The Bio-HEAT data-collection tools, Land-Surface Temperature Data and other environmental data platforms have already been established within the HEAT Center. Equally, the Bio-HEAT findings around potential protective interventions will directly inform the design of heat-health adaptive interventions to be tested in the HEAT Center and HIGH Horizons projects. Several of the investigators in Bio-HEAT work across all the projects, ensuring the seamless transfer of knowledge across the biological-causal modelling-adaptation-policy pathways in these projects. Wits Health Consortium ensures that there is no commitment or budgetary overlap in concurrent projects. The Consortium has separate, detailed budgets for each project with periodic review of cost allocations and expenditure, and distinct work plans for all concurrent projects, with clear allocation of activities and resources, and develop and implement a comprehensive monitoring and evaluation plan for finances and activities of each of project.

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12. Coapplicant details

1

Coapplicant	
Full Name	Prof Clive Gray
Department	Biomedical Sciences
Organisation	Stellenbosch University

Career history (current/most recent first)			
From	**To**	**Position**	**Organisation**

Career history (current/most recent first)			
From	**To**	**Position**	**Organisation**
04/2021	12/2026	Professor of Immunology in Molecular Biology and Human Genetics	Stellenbosch University
01/2011	03/2021	Professor and Chair of Immunology	University of Cape Town
08/2003	12/2026	Adjunct Professor	Duke University
05/1998	11/2010	Chief Specialist Scientist	National Institute for Communicable Diseases
01/1996	04/1998	Post Doctoral Fellow	Stanford University
11/1993	12/1995	Lecturer	University of the Witwatersrand
02/1985	10/1993	Research Officer	University of the Witwatersrand

Education/training				
From	**To**	**Qualification**	**Subject**	**Organisation**
11/1989	12/1994	Doctor of Philosophy (PhD;DPhil)	Immunology	University of the Witwatersrand
01/1986	12/1987	Master of Science (MSc)	Immunology	University of the Witwatersrand
10/1980	06/1984	Bachelor of Science (BSc)	Applied Biological Sciences	Bristol Polytechnic

Career breaks Have you taken any breaks from research that you wish us to take into consideration? This can include periods of parental or long-term sick leave, caring responsibilities, part-time work, secondments, volunteering or time spent in different sectors. You can also include any periods where you were unable to work because of the COVID-19 pandemic.	No

Do you wish to undertake this award part time? If you wish to undertake this award part-time, either from the start or part way through the grant, your host organisation must employ you on a part-time basis during that time.	No

Source(s) of personal salary support State all your sources of salary funding (for example, through your organisation's block grant from a higher education funding body), and the percentage of your salary they contribute. Answer 'not applicable' if you are not currently employed.
Stellenbosch University (Tenured)

Are you a healthcare professional?	No

Career contributions

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In relation to this application, summarise what you consider to be your key experience and achievements/contributions (e.g. publications, patents, impacts on policy). For each, provide details of when it came about, why you think it is important and what impact it has had.

Since 2018, I have conceived and secured seven international competitive grants on maternal-child health and investigations into immune pathways that affect neonatal and paediatric immune development. These grants include awards from the NIH, Canadian Institutes of Health Research, the Academy of Medical Sciences and the National Institute of Health Research. I also have an NIH-funded training grant on reproductive immunology and child development in the first 1000 days. I am spearheading an initiative to create reproductive immunology as a post-graduate Diploma and for training young clinical researchers in laboratory research on maternal and child immune health. I have made major contributions to knowledge on linkages between maternal health during pregnancy, especially in those women with HIV, and the reason why children born to these mothers have poor health. I have already shown that long-term antiretroviral use, given prior to conception, is detrimental to placental development and is a trigger for preterm birth and low birth weight. I have also shown that maternal immune events during gestation is reflected in the placenta, which carries a footprint of maternal immunity in the absence of vertical HIV transmission. I have also led teams investigating T cell immunity to HIV and TB over the past 25 years and was the Director of the regional laboratory of the HIV Trials Network in Southern Africa for 9 years. I was the first to publish on the restorative effects of antiretroviral therapy on host immunity and to show that the immune system is plastic in nature. I now Direct the Reproductive Immunology Research Consortium in Africa, where we investigate all aspects of infectious diseases and environmental influences on child immune development. Over the past 20 years, I have published more than 130 journal articles or book chapters, with an H-Index of 37. I direct an online immunology knowledge hub, Immunopaedia, which is used by the International Union of Immunology Societies (IUIS) for immunology courses I lead around Africa and Latin America.

Describe your approach to developing and supporting a positive and inclusive working/research culture, including examples from previous and current groups.
This could include, for example:

- mentoring
- supporting collaboration and interdisciplinarity
- leadership and people management
- promoting research integrity.

I believe in an all-inclusive leadership and to adapt in an organic flexible manner. Organic means that I listen to how best to improve the group and research culture. This may mean changing how we operate to adapt to changes in our environment, such as with clinical and patient recruitment. I am flexible in changing how the research may be performed, but staying focused on the topic and research question. I mentor each person in the group on a 1:1 basis. This is regardless of position and there is no hierarchy in my research group. I believe in promoting an open forum and also promoting students, post-doctoral fellows and early career researchers so that they attain their goals. I achieve this through behind the scenes mentoring and facilitating scientific discourse led by the staff, student or early career fellow. Being a highly collaborative scientist myself, I foster this ethos within the group and encourage junior scientists and post-docs to be open and collegial with those that we collaborate with or hope to collaborate with. In terms of integrity, this is the most important aspect of all the research my group performs and consists of three elements: Ethics, scientific rigour and honesty. Ethics: we adhere closely to all guidelines of our local and international committees. Scientific Rigour: all our assays, methods and storage of samples are fully optimised and validated. Honesty: this is managed through weekly work-in-progress meetings where each researcher presents raw data and how they processed the data for presentations.

I have led research groups since 1998 that has focused on HIV immunology, firstly at the National Institute for Communicable Diseases. I became Chair of Immunology at the University of Cape Town in 2011 and led the Division of Immunology for 10 years – enabling Immunology to fall within the top 50 ranking disciplines Worldwide. I then established the Reproductive Immunology Research

Preview mission

Consortium in Africa at Stellenbosch University in 2021, now leading a group of 12 researchers. My collaborations with top immunologists in Europe and North America allow my team to perform cutting edge research on maternal, placental and paediatric immunology. I have been awarded seven research and training grants from the NIH, European Commission and Canadian Institute of Health Research over the past three years, enabling my group to probe the impact of maternal health on child immune development.

Over the past 10 years I have supervised 6 BSc Hons students, 13 MSc students (2 current)), 11 PhD students (2 current), 13 post-doctoral Fellows (2 current). My role as a supervisor is to provide oversight of the scientific agenda in their respective research protects, while also facilitating an environment to develop as independent scientists. Apart from my formal academic role as research supervisor, I also frequently hold small immunology workshops across Africa, mentoring scientists across the continent. My support also extends to international activities, where, for example, I am the Vice Chair of the Education Committee of the International Union of Immunology Societies.

2

Coapplicant	
Full Name	Dr Renate Strehlau
Department	Paediatrics and Child Health
Organisation	Wits Health Consortium (Pty) Ltd

Career history (current/most recent first)			
From	**To**	**Position**	**Organisation**
01/2012	01/2027	Honorary Lecturer	Faculty of Health Sciences, University of the Witwatersrand
01/2007	12/2027	Medical Officer	Wits Health Consortium (Pty) Ltd
01/2007	12/2027	Site Principal Investigator and Deputy Director	Faculty of Health Sciences, University of the Witwatersrand
01/2006	11/2006	Forensic Medical Examiner	Avon and Somerset Constabulary, South West England
01/2005	12/2005	Community Service Medical Officer	South African Department of Health
01/2004	12/2004	Medical Intern	South African Department of Health

Education/training				
From	**To**	**Qualification**	**Subject**	**Organisation**
06/2017	06/2021	Doctor of Philosophy (PhD;DPhil)	Paediatric Neurodevelopment	Faculty of Health Sciences, University of the Witwatersrand
01/2011	06/2013	Master of Science (MSc)	Paediatric Neurodevelopment	Faculty of Health Sciences, University of the Witwatersrand
11/2007	05/2008	Diploma in Child Health	Child Health	The College of Medicine, South

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Education/training				
From	**To**	**Qualification**	**Subject**	**Organisation**
				Africa
01/2007	10/2007	Diploma in HIV Management	HIV Management	The College of Medicine, South Africa
01/1998	12/2003	Primary Med Qual (BM;MBChB;MBBS;MD)	Medical degree	Faculty of Health Sciences, University of the Witwatersrand

Career breaks Have you taken any breaks from research that you wish us to take into consideration? This can include periods of parental or long-term sick leave, caring responsibilities, part-time work, secondments, volunteering or time spent in different sectors. You can also include any periods where you were unable to work because of the COVID-19 pandemic.	No

Do you wish to undertake this award part time? If you wish to undertake this award part-time, either from the start or part way through the grant, your host organisation must employ you on a part-time basis during that time.	No

Source(s) of personal salary support State all your sources of salary funding (for example, through your organisation's block grant from a higher education funding body), and the percentage of your salary they contribute. Answer 'not applicable' if you are not currently employed.
Wits Health Consortium

Are you a healthcare professional?	Yes

Indicate your healthcare profession
Medical graduate

Are you clinically active?	Yes

What is your specialty? If your specialty is not on the list, select 'Other' and specify.
Paediatric Immun, Infect Dis & Aller

Career contributions In relation to this application, summarise what you consider to be your key experience and achievements/contributions (e.g. publications, patents, impacts on policy). For each, provide details of when it came about, why you think it is important and what impact it has had.
During my early career as a researcher, I was involved in clinical trials thatfocused on infants who

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were newly diagnosed with HIV, examining a range of antiretroviral treatment options. Some of these clinical trials, especially Neverest 2 and Neverest 3, fundamentally changed policy on the prevention of mother-to-child-transmission (PMTCT) of HIV in South Africa and had a major influence on international paediatric HIV treatment guidelines. These trials involve the long-term follow-up of children exposed to HIV or antiretroviral drugs, which gave me the opportunity to establish a research career in monitoring the progression of young children living with HIV. In these cohorts I also investigated the impact of lifelong antiretroviral use on growth and development. I developed a specialised interest in the neurodevelopmental outcomes of children infected with HIV and those exposed, but uninfected.

I have been involved in over 30 clinical trials in total, including 20 as Principal Investigator. In this role, I have formed collaborations with multiple international partners, conducting trials with global impact in the fields of HIV paediatric and adolescent treatment, tuberculosis vaccines, and COVID-19 infection in pregnancy. The Bio-HEAT study involves different research questions to my previous work, but using similar methods, cohort construction and a similar study population (pregnant and postpartum women and infants). Analytical strategies are also similar, albeit with an environmental rather than drug exposure.

As the Deputy Director of the Rahima Clinical Trials Research Unit, I oversee all research projects conducted in the unit in which the Bio-HEAT study will be undertaken. To date, I have co-authored 77 academic publications (ORCID ID 0000-0001-9113-6584, H-index 23). Being in this position and having extensive clinical trials expertise makes me well-suited to work together with the investigators involved in this grant application. My unit has a new suite of studies on the safety and efficacy of maternal vaccines and novel treatment agents for diseases such as Group B Streptococcus. As noted above, the procedures in these studies are very similar to those proposed in Bio-HEAT, allowing for the efficient use of staff.

Describe your approach to developing and supporting a positive and inclusive working/research culture, including examples from previous and current groups.
This could include, for example:

- mentoring
- supporting collaboration and interdisciplinarity
- leadership and people management
- promoting research integrity.

My leadership style is based on a deliberate strategy of leading from the front and by example, including through direct involvement in the full spectrum of research activities. I manage a team of 16 members (12 female, 81% non-white). As both a clinician and a scientist, I actively participate in clinical study procedures, while also leading data analysis and knowledge dissemination. This direct involvement with participants means that I can interact closely with all study staff and lead the project from recruitment, through to follow-up, and study finalisation with data interpretation and dissemination.

I strongly believe in actively developing the career paths of all employees through teaching, training, providing opportunities for academic engagement and up-skilling. Staff development activities include on-the-job mentoring and classroom sessions, including lecturing and supervision at Masters' level (six completed and three underway). I have made a point of helping advance junior researchers by including them as investigators on studies and providing them with opportunities to lead manuscript writing. This and other aspects of my leadership have translated into very high levels of staff retention, with many staff members having been retained for over ten years. Team members' roles evolve progressively over the years as they acquire new skills and grow into different leadership roles.

By using an open, direct and fair management style, I have managed to build tightknit teams. This approach has resulted in hard-working colleagues who show responsibility and take deep pride in

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their work.

A major strength of our research unit is its diversity. Including employees from a wide range of socioeconomic, cultural and educational backgrounds has deeply enriched the team and has, in large part, accounted for our success to date. The team, for example, is able to engage with research participants in their mother tongue and in a culturally-sensitive manner, enhancing the quality of the data received. Our closeness to participants and the community has been key to achieving high levels of cohort retention, far exceeding that of most research units. For example, we retained, 97% of participants at 56 weeks in one study (292/300; Strehlau, 2018) and 98% at 48 weeks in another (292/298; Murnane, 2017).

Practically, my leadership and mentoring approach involves monthly one-on-one meetings to support key performance areas, career development, and succession planning, partnering of early-career staff member with more experienced staff, and identifying and enrolling staff in relevant training programmes to build capacity.

To provide oversight and promote accountability among the team, I convene regular operational meetings to monitor team performance, including process and outcome indicators of our work. To uphold research integrity, we have set up systems to allow for independent review of research outputs, leveraging expertise within the Steering Committee and the Scientific Advisory Board as required.

I strive to instill a deep appreciation of research integrity among my staff. Staff frequently attend training in research ethics and Good Clinical Practice. I am convinced that, as in our work to date, my team will conduct the Bio-HEAT study according to the highest ethical standards.

3

Coapplicant	
Full Name	Dr Amy Wise
Department	Obstetrics and Gynaecology
Organisation	University of the Witwatersrand

Career history (current/most recent first)			
From	**To**	**Position**	**Organisation**
04/2021	12/2027	Acting Head, Department Obstetrics and Gynaecology	Rahima Moosa Mother & Child Hospital, Johannesburg
10/2015	12/2027	Senior Specialist, Obstetrics and Gynaecology	Rahima Moosa Mother & Child Hospital, Johannesburg
06/2011	09/2015	Junior Specialist, Obstetrics and Gynaecology	Rahima Moosa Mother & Child Hospital, Johannesburg
06/2009	05/2011	Senior Medical Officer	Rahima Moosa Mother & Child Hospital, Johannesburg
01/2005	05/2009	Registrar	University of the Witwatersrand
01/2004	12/2004	Junior Medical Officer	Charlotte Maxeke Hospital, Johannesburg
01/2003	12/2003	Community Service Officer	Chris Hani Baragwanath Hospital

Pre-submission

Career history (current/most recent first)			
From	**To**	**Position**	**Organisation**
01/2002	12/2002	Intern	Livingstone Hospital, Eastern Cape

Education/training				
From	**To**	**Qualification**	**Subject**	**Organisation**
01/2017	12/2022	Master of Science (MSc)	Research	University of the Witwatersrand
01/2015	12/2019	Certificate in Maternal and Fetal Health	Maternal and Fetal Health	College of Medicine, South Africa
11/2014	11/2015	Advanced Certificate in Health Management	Health Care Management	Foundation for Professional Development
01/2013	06/2013	Diploma, HIV management	HIV	College of Medicine, South Africa
01/2005	12/2010	MMed	Obstetrics and Gynaecology	University of the Witwatersrand
01/2005	12/2010	FCOG	Obstetrics and Gynaecology	College of Medicine, South Africa
01/1996	12/2001	Primary Med Qual (BM;MBChB;MBBS;MD)	Bachelor of Medicine and Surgery	University of the Witwatersrand

Career breaks Have you taken any breaks from research that you wish us to take into consideration? This can include periods of parental or long-term sick leave, caring responsibilities, part-time work, secondments, volunteering or time spent in different sectors. You can also include any periods where you were unable to work because of the COVID-19 pandemic.	No

Do you wish to undertake this award part time? If you wish to undertake this award part-time, either from the start or part way through the grant, your host organisation must employ you on a part-time basis during that time.	No

Source(s) of personal salary support State all your sources of salary funding (for example, through your organisation's block grant from a higher education funding body), and the percentage of your salary they contribute. Answer 'not applicable' if you are not currently employed.
Department of Health, Gauteng

Are you a healthcare professional?	Yes

Indicate your healthcare profession

Pre-submission

Medical graduate

Are you clinically active?	Yes

What is your specialty? If your specialty is not on the list, select 'Other' and specify.
Obstetrics & Gynaecology

Career contributions In relation to this application, summarise what you consider to be your key experience and achievements/contributions (e.g. publications, patents, impacts on policy). For each, provide details of when it came about, why you think it is important and what impact it has had.
I am a committed clinician with considerable research experience in clinical settings. My research project for my subspeciality in materno-foetal medicine focused on Doppler studies in foetuses and the prediction of poor outcomes in a real-world setting (the study site). The conclusion was that the use of the cerebro-placental ratio in early labour could not be used to predict which women were more likely to have an adverse birth outcome. The occurrence of these adverse outcomes likely involved multiple causal pathways and factors, as in the exposure-outcome relations studied in the Bio-HEAT project. The experience in my subspeciality research and my subsequent foetal medicine practice have made me highly proficient in Doppler and other sonography methods. This is particularly relevant for the proposed work in Bio-HEAT on maternal-foetal dyads in the context of climate change and heat exposure. Similarly, I was the study doctor on a nutrition-in-pregnancy project with similar sonar methods, and schedule of study visits and investigations as planned in the Bio-HEAT study. Additionally, my previous research experience makes me well suited to coordinate and oversee the management of a cohort within the clinical context. Our research activities in clinical settings are done jointly by clinical staff and research teams, with seamless links between these two groups. Several ongoing research projects involve close collaborative work, which has been highly successful. I have worked as co-Principal Investigator for a Point-of-Care device for diagnosing syphilis in conjunction with Burnett University, Australia, gaining much experience in participant recruitment. Being embedded in the public health system and having a deep knowledge of the environment and government processes has been a critical element in ensuring high-quality research implemented in a busy clinical setting. My research work has resulted in 16 publications on various aspects of high-risk obstetrics (ORCHID no: 0000-0001-5182-9060).

Describe your approach to developing and supporting a positive and inclusive working/research culture, including examples from previous and current groups. This could include, for example: • mentoring • supporting collaboration and interdisciplinarity • leadership and people management • promoting research integrity.
I was the lead of the Obstetrics and Gynaecology Department throughout the COVID-19 pandemic, while at the same time initiating and participating in several studies. That challenging period honed my leadership skills and helped me develop a tight-knit team. As a female leader from a background of privilege, I am aware of my responsibility to promote equity among my staff. South Africa is among the most unequal societies globally across many measures, including gender. I am thus especially sensitive to the need to recruit and mentor young women and other marginalised groups. My leadership has been critical to enhancing equity and ensuring equal opportunities for staff. As the Acting Head of the Department of Obstetrics and Gynaecology, I have overseen the recruitment of six consultants, who are all young, and the majority female and African.

Resubmission

Additionally, I recruited six medical officers with a similar demographic profile.

I have made a point of ensuring that early-career clinical staff are exposed to research processes, and have used research projects as an opportunity to train staff in new procedures or topics. Bio-HEAT provides many such opportunities. Specific activities include:

· Quarterly meetings with each staff member to review key performance areas and facilitate their progression

· Identifying staff with key skill sets and partnering them with more senior staff to ensure knowledge and skills transfer

· Identifying and enrolling staff in relevant training programmes to build capacity

· During ultrasound procedures in the Bio-HEAT study, providing the on-the-job teaching of ultrasound skills, interpretation and clinical application

Within the busy and stressful clinical environment, I facilitate and encourage communication among all health workers, regardless of grade or cadre. I have maintained good working relationships with the research team at the site, and avail myself or members of my team to be of assistance at any time. Additionally, within the hospital environment, there is an established relationship with the Psychology Department, which conducts regular staff debriefings. I encourage staff to attend debriefings and have received positive feedback on their experiences. Obstetrics and Gynaecology can be a challenging discipline – learning to deal with a family's grief over a poor outcome and the loss of a baby or mother is a skill that takes time to acquire. I support more junior colleagues through this and accompany them to attend difficult meetings. Research staff work closely with participants who have complex psycho-social circumstances and may have poor outcomes.

I make a point of commending people on the cases they have managed and research work they have done. I actively look for articles and courses, and arrange workshops that are relevant to the diverse interests within my Department.

I am committed to building a culture of research and academic excellence within the Department. With two research units at the hospital, there are many opportunities to nurture junior colleagues and capacitate them with research skills to further their careers and make a meaningful impact on the health of women and children in the face of the rapidly-escalating climate crisis.

Pre-submission

13. Costs requested and justification

Select the currency in which you want to apply. Submit costs in the currency you think will best enable you to undertake the activity. This will probably be your local currency; if not, explain why not.
GBP - Pound Sterling

Is this your local currency?	No

What is your local currency?	ZAR

Explain why you are requesting costs in the selected currency and what exchange rate you have used.

We have requested the budget in Pounds Sterling as the currency in South Africa (South Africa Rand) fluctuates considerably against the Pound. Requesting costs in a more stable currency allows us to provide more predictable amounts for project costs.

We have used an exchange rate of Rand 19 to £1, which reflects the present exchange rate and the rate in recent months

Staff Are you requesting staff?	Yes

Staff

Cost type	Number of staff requested for	Staff category	Name (if known)	Basic starting salary (p.a.)	Salary grade / scale	Period on project (months)	% time	Total (£)
Salary	1	Lead Applicant Wits RHI	Matthew Chersich	122,845	D4	42	20	92,849
Salary	1	Co-Lead & Director Wits RHI	Gloria Maimela	142701.86	D5	42	10	53,928
Salary	1	Director Assistant Wits RHI	TBC	44937.66	C4	42	10	16,982
Salary	1	Social Scientst Wits RHI	TBC	70404.81	C3	42	10	26,607
Salary	1	Executive Director Wits RHI	Helen Rees	196997.70	D4	42	2	14,890
Salary	1	Executive Assistant Wits RHI	Karen Cornell	77115.67	D2	42	2	5,829
Salary	1	Senior Researcher Wits RHI	TBC	61035.25	D2	42	100	230,658
Salary	1	Senior Programme Manager Wits RHI	TBC	61035.25	D2	42	10	23,066
Salary	1	Portfolio Manager Wits RHI	Zororo Mavindidze	85680.87	D2	42	5	16,190
Salary	1	Principal Investigator RCT	Renate Strehlau	76315.79	D4	42	10	28,841
Salary	1	Medical Officer RCT	Karl Technau	76315.79	D4	42	20	57,681
Salary	1	Medical Officer	Amy Wise	76315.79	D1	42	15	43,261

Pre-submission

Cost type	Number of staff requested for	Staff category	Name (if known)	Basic starting salary (p.a.)	Salary grade / scale	Period on project (months)	% time	Total (£)
		RCT						
Salary	1	Qualitative Researcher RCT	TBC	39157.89	C5	42	3	17,130
Salary	1	Laboratory Technician RCT	TBC	15789.47	B5	42	25	14,918
Salary	1	Enrolled Nurse RCT	TBC	14526.32	B5	42	50	27,448
Salary	1	Regulatory Officer RCT	TBC	12631.58	C1	42	30	14,321
Salary	1	Study Administrator RCT	TBC	15789.47	B1	42	30	17,901
Salary	1	Research Assistant 1 RCT	TBC	7578.95	C1	42	25	7,160
Salary	1	Research Assistant 2 RCT	TBC	7578.95	C1	42	25	7,160
Salary	1	Data Capturer RCT	TBC	9473.68	B2	42	50	17,901
Salary	1	Physiotherapist RCT	TBC	39157.89	C3	42	5	8,565
Salary	1	Dietician & Breastfeeding Counseling RCT	TBC	39157.89	C3	42	2	2,960
Salary	1	Immunologist SU	Clive Gray	169000	D5	42	10	31,132

Pre-submission

Justification for staff
Specify the role and responsibilities for the staff requested. Justify the type and seniority, including the level of salary requested, of each post.

Wits RHI

Matthew Chersich, Lead Applicant, 20% (LOE) £92,849
Overall responsibility for coordination, leadership and technical oversight
Gloria Maimela, Director of Climate and Health, 10% £53,928
Implementation oversight and engagement with policy makers
TBC Senior Researcher, 100% £230,658
Research outputs and study management
Helen Rees, Executive Director Wits RHI, 2% £14,890
Expert advisor

Karen Cornell, Executive Assistant Wits RHI, 2% £5,829
Expert advisor assistant
Zororo Mavindidze, Portfolio Manager, 5% £16,190
Compliance support
TBC, Director Assistant, 10% £16,982
Administration support to Lead and Co-applicants
TBC, Social Scientist, 10% £26,607
Conduct social science components of study
TBC Senior Programme Manager, 10% £23,066
Overall project management

Rahima Clinical Trials

Renate Strehlau, Co-applicant, 10% £28,841
Principal Investigator, study implementation and oversight of the cohort
Karl Technau, 20% £57,681
Head of Empilweni Clinic and lead on the design, conduct and analysis of the social science activities
Amy Wise, 15% £43,261
Responsible for research activities in the clinical setting
TBC Qualitative Researcher, 10% £17,130
Designing and setting up tools for social science activities, and assessing mental health and psycho-social conditions
TBC Laboratory Technician, 25% $14,918
Sample processing and maintaining sample integrity
TBC Enrolled Nurse, 50% £27,488
Participant enrolment and clinic follow-up visits
TBC Regulatory Officer, 30% £14,321
Frequent communication with ethics including notification of Serious Adverse Events
TBC Study Administrator, 30% £17,901
Co-ordination between members of study team and management
TBC Research Assistant (1), 25% £7,160
Participant recruitment and retention
TBC Research Assistant (2), 25% £7,160
Participant recruitment and retention
Data Capturer, 50% £17,901
Real time, contemporaneous, high-quality capturing of data
Physiotherapist, 5% £8,565
For newborn care, when required
Dietician and Breastfeeding Counselling, 2% £2,960
Counselling and support for pregnant mothers to perform exclusive breastfeeding

Stellenbosch University

Clive Gray, Co-applicant, 10% £31,132
Oversee laboratory testing and immunology topic areas

Pre-submission

Adjustment support Are you requesting adjustment support?	No

Training and continuing professional development Are you requesting training and continuing professional development?	Yes

Training and continuing professional development

Cost type	Description	Total (£)

Cost type	Description	Total (£)
Research skills training	Research Team Training	3,158
Continuing professional development and professional skills training	Skills Development Training	4,810
Continuing professional development and professional skills training	Capacity Building	4,210

Justification for training and continuing professional development.
We are requesting funds for the following capacity development activities: 1. Research Team training for project implementation: £3,158 in Year 1 2. Wits Health Consortium provides Skills Development Training for employees £4,810 (£12,72 x 9 staff per month x 42 months). This is a per person staff development cost to enhance staff core skills and competencies. 3. Capacity building: short course or secondment of study personnel at Rahima Clinical Trials to enhance skills and capabilities that are required for the fulfilment of study activities: £2,105 in Year 1 and Year 3.

Materials and consumables Are you requesting materials and consumables?	Yes

Materials and consumables

Description	Total (£)
Water Bottles	434
Archiving	11,579

Justification for materials and consumables.
We are requesting funds for the following materials and consumables: 1. Water bottle for women during labour as they often cannot leave their beds to obtain water: £1.97 per bottle x 220 participants. Total £434 2. Archiving of patient files: £2.506 per participant (220) x 21 years as per South African law. Total £11,579

Animals Are you requesting animals?	No

Pre-submission

Equipment Are you requesting equipment?	Yes

Equipment

Type	Type of equipment	No. of items	Cost per item	Cost of maintenance contract	Contribution from other sources	Total (£)
Equipment purchase	Laptops	5	1105	0	0	5,525
Equipment purchase	Indoor Temperature Monitors	40	26	0	0	1,040
Equipment purchase	Wearable Temperature Monitors	225	34	0	0	7,650
Equipment purchase	Swallowable Temperature Monitors	60	79	0	0	4,740
Equipment purchase	Temperature Probes & Installation	1	930	0	0	930
Equipment purchase	Fitbit monitors	225	158	0	0	35,550
Equipment purchase	HEAT Adaptation Equipment	1	21053	0	0	21,053
Equipment purchase	Quick Scan Handheld Ultrasound	3	3881	0	0	11,643

Justification for equipment.
1. 5 Laptops for study work £5,525 • 3 for Wits RHI at £1105 each • 2 for Rahima Clinical Trials at £1105 each 2. 40 Indoor Temperature monitors for Rahima Clinical Trials to monitor air temperature and humidity at £26 each, total £1,040 3. 225 Wearable Temperature monitors for Rahima Clinical Trials at £34 each, total £7,650 4. 60 Swallowable Temperature monitors for Rahima Clinical Trials at £79 each, total £4,740 5. Temperature Probes & Installation for the labour ward £930 6. 225 Fitbit monitors at £158 each, total £35,550 7. Provision is made for HEAT adaptation Equipment for the labour ward at Rahima Clinical Trials £21,053 8. 3 Quick Scan Ultrasound Handheld Devices (includes Samsung tablet to operate) at £3881 each, total £11,643

Are you requesting a piece of equipment with a list price of £100,000 or more?	No

Pre-submission

Access charges Are you requesting access charges?	No

Overheads Are you requesting overheads?	Yes

Overheads

Description	Total (£)
Wits Health Consortium	327,107
Stellenbosch University	6,226

Justification for overheads.

Overhead for WHC includes: WHC, Wits RHI and Rahima Clinal Trials. Total £327,107 - Support Letter included

1. WHC overhead £163,554

WHC provides a shared services centre with financial, contractual, compliance, payroll and human resource expertise.
• Contract management £8,017 (contract administration and management)
• Legal advice and support £3,207 (agreement review, legal arrangements for grants, and drafting of sub-award agreements)
• Financial function (bookkeeping, grant management, financial management and system management and Compliance. Includes computerized accounting systems, procurement system and installation of software, troubleshooting problems as well as technical support.) £96,207
• Human resource management (full function support, recruitment, performance management, probation, induction, general human resource queries, employee grievances, new starters, and terminations) £32,069
• Payroll management (end to end processing, maintenance of payroll system. Updating payroll records and liaising with staff and management on payroll queries, leave and overtime.) £24,052

2. Wits RHI & Rahima Clinical Trials Overhead £163,553

• Procurement (Obtaining cost estimates, capturing of orders and ensuring delivery.) £26,169
• Rental, Building Maintenance and Security (Maintaining facilities, repairs and cleaning and providing a safe work environment) £57,244
• Security (includes armed response and guards) £14,720
• IT/Internet/Email/WiFi/Software Costs (Network bandwidth, email accounts, software licenses, PC user technical support and network administration as well as virus protection.) £65,421

3. Stellenbosch University Overhead £6,226 Support Letter Included

• Financial management £398.46
• HR £790.70
• Legal £24.90
• Other central divisions £205.46
• IT £367.33
• Strategic Fund £622.60
• Audit Fees & Insurance £84.05
• Central facility fee £896.54
• Library £694.20
• Intellectual Property Support £21.79
• Research Support £358
• Laboratory and office space £1761.96

Pre-submission

Upload a letter from the Finance Director of each organisation. If there is more than one letter, upload these as a single PDF. Each letter must include: • a full breakdown of costs requested (you can't ask for a percentage of the project costs) • an explanation of why these costs are necessary for the project • confirmation that the breakdown is a true representation of the costs incurred.
(overheads letter PDF - WT Indirect Cost Letters.pdf) is included as an appendix within this file.

Are you based at a UK university and requesting overheads on subcontracted costs?	No

Travel and subsistence Are you requesting travel and subsistence?	Yes

Travel and subsistence

Type	Description	How much carbon will this offset (in tonnes)?	Total (£)
Other travel	International Airfare		18,358
Other travel	International Accommodation		11,474
Other travel	International Per Diem		9,716
Other travel	International Ground Travel		505
Other travel	Internation Visa's		229
Other travel	Local Airfare		2,054
Other travel	Local Accommodation		6,631
Other travel	Local Per Diem		2,270
Other travel	Local Ground Travel		525

Justification for travel and subsistence.

Pre-submission

1. International Airfare £18,358
Wits RHI £11,474 (10 flights over 3.5 years at £1,147.40 per flight)
Rahima Clinical Trials - £6,884 (6 flights over 3.5 years at £1,147.33 per flight

2. International Accommodation £11,474
Wits RHI - £7,171 (25 nights over 3.5 years at £286.84 pn)
Rahima Clinical Trials - £4,303 (15 nights over 3.5 years at £286.84 pn)

3. International Per Diem £9,716
Wits RHI - £6,072 (25 days at £242.89 per day)
Rahima Clinical Trials - £3,643 (15 days at £242.89 per day)

4. International Ground Travel £505
Wits RHI - Airport Transfers/Uber £316 (5 transfers over 3.5 years at £63.11 per trip)
Rahima Clinical Trials - Airport Transfers/Uber £189 (3 transfers over 3.5 years at £63.11 per trip)

5. International Visa's £229 at £28.68 x 8 Visa's

6. Local Airfare £2,054
Wits RHI team between Cape Town & Johannesburg (4 flights py x 3.5 years at £146,69 each)
7. Local Accommodation £6,631
Wits RHI team between Cape Town & Johannesburg (4 nights quarterly x 3.5 years at £118.41 pn)
8. Local Per Diem £2,270
Wits RHI team between Cape Town & Johannesburg (5 days quarterly x 3.5 years at £32.43 pd)
9. Local Ground Travel £525
Wits RHI team between Cape Town & Johannesburg (4 trips py x 3.5 years at £37.50 per trip)

Overseas allowances Are you requesting overseas allowances?	No

Fieldwork expenses Are you requesting fieldwork expenses?	Yes

Fieldwork expenses

Description	Total (£)
Tablets	1,711
Clinic Supplies	3,158
Printing Study Material	2,625
Transport for Fielwork	2,776
Data Costs	4,021
Recruitment & Retention	21,684
Participant Costs	53,668
Data Analysis	1,863
Translations	2,368

Justification for fieldwork expenses.

Pre-submission

1. 5 x Tablets at £342 for Fieldworkers, Total £1,711
2. Clinical Supply Costs at £185.76 pm x 17 months, Total £3,158
3. Printing of study related material at £62.49pm x 3.5 years, Total £2,625
4. Transport for home visits and follow ups at £4.33 per visit x 2 staff x 4 visits x 80 patients, Total £2,776
5. Data costs for connectivity and community engagement at £95,75 pm, Total £4,021
6. Recruitment and retention activities £1,276 pm x 17 months, Total £21,684
7. Participant costs – Reimbursements at £21.684 per visit x 220 participants x 10 visits each, Total £47,705 and Refreshments at £2.71 per visit x 220 participants, x 10 visits each, Total £5,963
8. Data analysis £1,863
9. Translation of study material to Zulu, Sotho and Afrikaans £2,368

Clinical research Are you requesting clinical research?	Yes

Clinical research

Description	Total (£)
Laboratory Costs	150,526
Ultrasound Costs	62,613
Genetics tests RNA Analysis	64,842
Immunology Marker IL6	9,842
Laboratory Storage Costs	52,632
Morphology Assessments	5,263

Justification for clinical research.

1. Laboratory Costs at £684.21 per participant, x 220 participants, as per protocol objectives for blood samples, test kits, biological tests, and field supplies, Total £150,526
2. Ultrasound Costs at £56.92 per scan, x 5 scans per participant x 220 participants, Total £62,613
3. Genetic tests RNA Analysis Costs at £147.37 x 2 tests per participant, x 220 participants, Total £64,842
4. Immunology Marker IL6 Costs at £22.37 x 2 tests per participant, x 220 participants, Total £9,842
5. Laboratory Storage Costs at £239,23 x 220 participants, Total £52,632
6. Morphology Assessments £5263

Public engagement and patient involvement Are you requesting public engagement and patient involvement?	Yes

Public engagement and patient involvement costs

Description	Total (£)
Co-Design interventions and workshops	4,211
Community Advisory Board	7,442
Regulatory & Ethics	2,179
Dissemination	6,781

Pre-submission

Justification for public engagement and patient involvement.
1. Co-design interventions and workshops £4,211 Rahima Clinical Trials x 3 workshops with health workers at £1,404 per workshop to design the labour ward interventions 2. Community Advisory Board meetings £7,442 Rahima Clinical Trials x 7 meetings at £26.58 per CAB member, 40 CAB Members 3. Regulatory & Ethics applications and annual fees £2,179 Rahima Clinical Trials at £1,394 Year 1 (application and amendments), £363 Year 2 and 3, and £58 Year 4 4. Dissemination £6,781 Rahima Clinical Trials: £28.25 x 200 Participants and x 40 CAB members

Contract research organisations Are you requesting contract research organisations?	No

Other Are you requesting other?	Yes

Other

Type	Description	Total (£)
Conference/seminar hosting	CHANCE Network	50,000
Consultancy fees	Dr Phelelani Mpangase	53,750
Consultancy fees	Dr Sibusisiwe Makhanya	53,750
Consultancy fees	Prof Shane Norris	53,750
Consultancy fees	Prof Justus Hofmeyr	53,750

Justification for other.
CHANCE Network activities involve stakeholder networking and regional climate change and health engagement between the study team and national policy makers and leading researchers Consultants 1. Dr Phelelani Mpangase will lead bioinformatics analyses of the RNASeq data 2. Dr Sibusisiwe Makhanya will lead climate science and forecasting activities and support geospatial analyses using the IBM Geospatial Data Analytics Platform and other spatial datasets 3. Prof. Shane Norris for technical inputs on foetal development 4. Prof. Justus Hofmeyr for expert inputs on intrapartum care and thermoregulation

Summary of costs requested	
	Total (£)
Staff	777,378

Pre-submission

Adjustment support	0
Training and continuing professional development	12,178
Materials and consumables	12,013
Animals	0
Associated animals costs	0
Equipment	88,131
Access charges	0
Overheads	333,333
Travel and subsistence	51,762
Overseas allowances	0
Fieldwork expenses	93,874
Clinical research	345,718
Public engagement and patient involvement	20,613
Contract research organisations	0
Other	265,000
Total	**2,000,000**

14. Full economic costing

Is your organisation based in the UK?	No

Pre-submission

15. Appendices

1) overheads letter PDF - WT Indirect Cost Letters.pdf

Pre-submission

WITS HEALTH CONSORTIUM

Wits Health Consortium (Pty) Ltd
Reg No.: 97/15443/07
Vat No.: 4310171493

Tel: +27 11 274 9200

31 Princess of Wales Terrace, Parktown,
2193, South Africa

Postnet Suite 189, Private Bag
X2600, Houghton, 2041

9 November 2022

Grants Adviser
Wellcome Trust
Gibbs Building,
215 Euston Road
London NW1 2BE, UK

Re: Wellcome Trust guideline for Indirect Costs

Wellcome Trust Guidance states that requests for indirect costs from low- and middle-income country institutions must be accompanied by a letter from the Finance Director of the institution, confirming the request is a true representation of the costs incurred. As Wits Health Consortium's Chief Financial Officer, I hereby confirm that the following support costs/ indirect costs are included in the proposal budget and are a true representation of the costs that will be incurred:

Support costs/Indirect Costs comprise of the following cost:

WHC - Wits RHI Indirect Costs				
Break down of costs			**TOTAL**	
Cost	**% effort**	**No of Months**	**GBP**	
Contracts Manager	5%	42	£	8,017.33
Legal Advisor	2%	42	£	3,206.93
Systems Manager	5%	42	£	8,017.33
Finance Manager	5%	42	£	16,034.66
Accountant	10%	42	£	24,051.99
Bookkeeper	5%	42	£	24,051.99
Finance Administrator	10%	42	£	16,034.66
Compliance Officer	5%	42	£	8,017.33
Human Resources Manager	10%	42	£	16,034.66
Human Resources Officer	5%	42	£	16,034.66
Payroll Supervisor	2%	42	£	8,017.33
Payroll Officer	5%	42	£	16,034.66
TOTAL			**£**	**163,553.51**

Finance Management, Legal , Payroll and HR
These costs are fees charged by WHC as the legal entity of for services provided to Wits RHI. WHC provides a shared services centre with financial, contractual, compliance, payroll and human resource expertise.

Pre-submission

Contracts Manager
The Contracts department is responsible for all contract administration and management.

Legal Advisor
Is responsible for review of agreements and legal arrangements for grants and drafting of subaward agreements

Systems Manager
Oversees the implementation of the computerized accounting system and the procurement system- installing software, updates and patches; troubleshooting problems; and providing technical support to financial staff.

Finance Manager:
Management of finance staff, reporting to donors, interface between central finance and division, donor audit management.

Accountant
Review of reports, processing of transactions, management of debtors and creditors , budget and expense analysis, periodic invoicing, financial reporting, payroll distribution changes and associated communications with customers, PI and sponsors; performs grant closeout functions required by Grants and Contracts Administration and sponsors including reconciliations, financial status reports, final invoices, purchase order liquidations, and final reporting; reviews general ledger transactions to ensure accuracy and complete journal entries.

Bookkeeper:
The bookkeeper records all the financial transactions that take place for project. Ensure all supplier invoices and accounts are paid, does the monthly bank reconciliations. He is also responsible for the filing and safekeeping of the source documents (such as invoices, receipts, or deposit slips) relating to these transactions. In addition to this, a bookkeeper might be required to perform a variety of administrative duties – such Asset verification.

HR Officer Full function support inclusive of recruitment, performance management, probation, induction, general HR queries, employee grievances, new starters, terminations, leave queries, HR Administration.

Payroll Supervisor - Reviews and verifies Payroll reports prepared by the payroll officer. Complies 3rd party payments and reports i.e Sars , Medical Aid ,Provident Fund etc . Supervises the maintenance of the Employee Information System. Preparation of IRP5's and IRP5 reconciliations.

Payroll Officer: - End to end processing of the project payroll (weekly, fortnightly and/or monthly). Maintenance of payroll system and leave planning system. Updating and maintaining payroll records. Liaising with staff and management on payroll related queries. Maintaining leave, sickness and overtime reports. Capturing of payments onto the online

Pre-submission

Wits RHI & Rahima Moosa Clinical Trials Other Support Costs			
Procurement Support	623.06	42	£26,168.56
Rental, Utilities , Furniture , Building Maintenance and Parking	1,362.95	42	£57,253.73
Security	350.47	42	£14,719.82
TOTAL			**£98,132.11**

Wits RHI & Rahima Moosa IT Support Costs			
IT/Internet/Email /Wifi/Software Costs	1557.65	42	£65,421.40
TOTAL			**£65,421.40**

Wits RHI & Rahima Moosa - OTHER SUPPORT COSTS

Procurement Support : The Procurement team assists in obtaining estimates for the costs of specific equipment, materials, goods, and services , Loading Orders on the procurement system and ensuring delivery from suppliers.

Rental , Utilities costs : The maintenance unit is responsible for maintaining facilities, repairs, cleaning and providing a safe working environment. The team is made up of a Facilities Manager, Receptionist, Supervisors and Assistants.
Costs for facilities includes basic rental of office space, water, rates and taxes, electricity, insurance and furniture.

Security : Includes armed response and security guards

Wits RHI & Rahima Moosa – IT SUPPORT COSTS

These costs include expenses for network bandwidth, email accounts/access, standard software licenses, PC user technical support, network administration and maintenance, virus protection and uninterrupted power supply where necessary and feasible.

Please do not hesitate to contact me should further information be required.

Sincerely,

Jéan Du Randt
Chief Financial Officer
Wits Health Consortium
Tel: +27 11 274 9200

Pre-submission

Stellenbosch
UNIVERSITY
IYUNIVESITHI
UNIVERSITEIT

FINANCES
KWEZEMALI
FINANSIES

10 November 2022

Wellcome Trust

Gibbs Building,

215 Euston Road

London NW1 2BE

UK

Pre-submission

RE: Indirect costs on Wellcome Trust Award - Prof Gray UNS141962

Stellenbosch University (SU) researchers are committed to making their expertise available to South African and international organisations. Research funding obtained in this way is managed by the University with the utmost diligence.

1. All university activities that are funded from outside funds are associated with certain indirect costs, and the motivation for the Indirect Cost Recovery Rate (ICRR) is to recover these indirect costs and thereby to manage the University as a financially sustainable enterprise.

   A further aspect contributing to the need for indirect cost recovery is the South African legislation with regards to intellectual property - the Intellectual Property Rights from Publicly Financed Research and Development Act, No. 51 of 2008 (hereinafter 'the IPR Act'). The IPR Act requires institutions that receive public funding to recover the full cost with regard to contract research.

   With reference to the abovementioned legislation, a national approach was designed and approved with regard to the calculation of the ICRR for all public higher education institutions in South Africa. SU uses the approved national formula and actual information from its financial statements to calculate the ICRR in an accurate and nuanced manner. The ICRR is recalculated and adjusted at least every two years. In 2017 a decision was made to review and revise the current ICRR policy and ICRR percentage. This amendment was approved and the new policy has been effective as of 1 January 2019.

2. External organisations regard universities with advanced applicable expertise as *valuable partners* in the attainment of their business objectives. In its credo SU presents itself as a

"knowledge partner", and as such it is committed to supporting, developing and expanding this level of interaction.

3. The following aspects were taken into account when establishing the ICRR and also in reviewing the ICRR policy and ICRR percentage:

   a) Research funded by outside funding creates *additional costs* for the University, which we refer to as "indirect costs" or "overheads". No provision is made for these extra costs within the funding received by universities from the state subsidy. These extra costs include covering services as listed in the below table:

Percentage split of Stellenbosch University ICRR	
- Human Resources (not direct staff costs on projects)	2.54%
- Legal Services	0.08%
- Other central service divisions	0.66%
- Finance	1.28%
- IT	1.18%
- Strategic Funds	2.00%
- Bank fees, audit fees, insurance, etc.	0.27%
- Central facility costs	2.88%
- Library	2.23%
- Support in managing matters regarding intellectual property	0.07%
- Research support services	1.15%
- Laboratory and office space	5.66%
ICRR (on income)	**20.00%**

   These "indirect costs" have to be recouped, in order to ensure that contract research is not being subsidized by other sources. This is currently achieved through applying an ICRR of 20% on all income from the third- and fifth streams of income, and 25% on direct costs. Gross third stream income includes research contracts and diverse research. Fifth stream income includes consultation services, routine services and the sale of all other products and services.

   b) Funding that is excluded from the ICRR is funding that is earmarked for bursaries (i.e. where funding was earmarked for bursaries from the outset) and undesignated donations.

Pre-submission

4. Based on the new overhead policy of the Wellcome Trust as of 1 October 2019, the overheads requested for the above-mentioned application will be 20% of GBP 31,132 (direct costs). Total overhead requested will amount to GBP 6,226 and this is a true reflection of the overhead cost to be incurred.

Enquiries about the ICRR should be directed to Ms Ilse Griffiths (wilters@sun.ac.za; 021 808 4539).

Kind regards

Mr HAJ Lombard
Chief Director: Finance

Pre-submission

Pre-submission

Hoofdirekteur: Finansies | Chief Director: Finance | uMlawuli oyiNtloko: kwezeMali
Privaat Sak X1, Private Bag X1, Matieland, 7602 | Private Bag x1, eMatieland,7602
Tel | Umnxeba: +27 21 808 4517 | www.sun.ac.za