IDDO DATA PLATFORM
DATA USE AGREEMENT

BACKGROUND:

(A) The Infectious Diseases Data Observatory (IDDO) has developed a collaborative data repository that standardises, secures, and makes available for research, global data on emerging and poverty-related diseases of public health importance. The Platform aims to reduce the impact of these diseases through rapid access and responsible reuse of data.

(B) IDDO is based at the University of Oxford where the Platform is hosted.

(C) The Data Access Committee or "**DAC**" is an independent group of experts appointed to review and make decisions regarding applications for access to data stored on the Platform by researchers and institutions. DAC membership, Terms of reference and decisions are available at https://www.iddo.org/data-sharing/accessing-data

(D) The Recipient wishes to access the Dataset for the purposes set out in the Application, which has been approved by the DAC. The Parties have agreed to enter into this Agreement which sets out the terms on which the Recipient may use the Dataset.

THIS AGREEMENT is effective as of the date of last signature ("Effective Date")

BETWEEN:

(1) **THE CHANCELLOR MASTERS AND SCHOLARS OF THE UNIVERSITY OF OXFORD,** whose administrative office is at University Offices, Wellington Square, Oxford, OX1 2JD, United Kingdom on behalf of the **Infectious Disease Data Observatory (IDDO)** and

(2) **WITS HEALTH CONSORTIUM (PTY) LTD** named on the signature page of this document

(the "**Recipient"**), (each a "**Party**" and together the "**Parties**").

FOR THE TRANSFER OF THE DATASET TO CONDUCT THE RESEARCH OUTLINED IN

SCHEDULE 2. NOW IT IS AGREED as follows:

1. DEFINITIONS

In this Agreement:

"**Applicable Regulations**" means all laws, regulations, regulatory requirements and authorisations, decisions and guidance of regulatory authorities or other requirements applicable in the context of this Agreement;

"**Application**" means the application submitted by the Recipient to access the Dataset as may be amended from time to time, a current copy of which is appended to Schedule 2;

"**Background IP**" means all Intellectual Property Rights held by a Party prior to receiving access to the Dataset;

"**Confidential Information**" means the Dataset and any and all information disclosed by or on behalf of IDDO at any time that would be regarded as confidential by a reasonable person or information which is identified as being confidential or otherwise designated to show expressly that it is imparted in confidence;

"**Data Contributors**" means the person(s) or institution(s) that provided the Dataset(s) as set out in Schedule 1;

"**Data Recipients**" or "**Recipients**" means the person(s) that are requesting the Dataset(s) as set out in Schedule 2;

"Dataset" means the data as may be amended from time to time, more particularly described in the version of Schedule 1 appended to this agreement. The Dataset is pseudonymised, meaning that individual-level data relating to a natural person within the Dataset is no longer identifiable from those data by virtue of omission, obfuscation or replacement with a safeguarded, non-identifiable code.

"**Derived Data**" means any data derived from use or analysis of the Dataset in the course of the Research and any collections of data, datasets and databases housing the foregoing and any database rights in or relating thereto;

"**IDDO Data Platform" or** "**Platform**" means the platform developed and maintained by the University of Oxford on which data are contributed by a variety of Data Contributors (including those listed in Schedule 1) are collated and curated;

"**Digital Object Identifier**" or "**DOI**" means a persistent identifier used to identify objects uniquely. In the context of the Platform, DOIs may be assigned to some or all of the Dataset(s) as set out in Schedule 1;

"**Enriched Data**" means any new or additional data that is collected by the Recipient for the purpose of the Research and which incorporates the Dataset (or any part thereof) and any collections of data, datasets and databases housing the foregoing and any database rights in or relating thereto;

"**Intellectual Property Rights**" means any and all patents, copyright, registered designs, design rights, trade marks, database rights, regulatory rights in data exclusivity and market exclusivity (including under Directive 2001/83/EC and any national implementing legislation), know how and any other intellectual property rights anywhere in the world in each case whether registered or unregistered, including any and all applications for such rights and the right to make such applications and all similar or equivalent rights or forms of protection which subsist or will subsist now or in the future in any part of the world;

"Publication" means any abstracts, reports, external communication, websites, presentations or peer-reviewed scientific publications that contain information, data or Research Results that are directly or indirectly related to the Dataset(s) and "**Publish**" shall be construed accordingly;

"**Research**" means the research to be performed by the Recipient as described in the Application;

"**Research Results**" means the results of the research performed by Data Recipients using the Data, including all Publications, Intellectual Property Rights, Derived Data and Enriched Data that are generated, or otherwise collected, arising, identified or first reduced to practice, in the course of research (but excluding the Data);

"**Research Team**" means the principal researcher and the individuals directly involved in the performance of the Research who are named on the Application;

"**Schedule**" means a schedule to this Agreement;

"**Term**" means two years after the execution of the DUA;

"**Third Party**" means any entity or person other than the Parties.

2. DATA TRANSFER

2.1 The University of Oxford shall provide the Dataset to the Recipient following execution of this Agreement by both Parties.

2.2 The Recipient has the right to use the Dataset solely for the purposes of the Research which shall be conducted by the Research Team. Subject to Clause 3.3.2, the Recipient is permitted to share the Dataset with other members of the Research Team solely for the purposes of the Research, including Research Team members who are not employees or students of the Recipient. Any subsequent analysis requires a new application.

2.3 Subject to Clause 2.2, the Recipient will not transfer the Dataset or otherwise make it available to any Third Party.

2.4 Nothing in this Agreement shall prevent the University of Oxford or the Data Contributors from being able to use the Dataset for any purpose, including but not limited to distribution of the Dataset to Third Parties for research purposes.

2.5 The Recipient acknowledges that it shall have no rights in or to the Dataset other than the right to use it in accordance with the express terms of this Agreement.

2.6 The Parties agree that following approval by the DAC, the Schedules to this Agreement can be updated and the most recent version of these Schedules appended to this Agreement as relevant without the need for a signed amendment to this Agreement.

3. RECIPIENT OBLIGATIONS

3.1 The Recipient acknowledges that the Dataset is pseudonymised and that the intention is that the University of Oxford shall not transfer, disclose or otherwise make available any personal data (as defined in the Data Protection Act 2018) to the Recipient. Notwithstanding, the Recipient shall immediately notify the University of Oxford if it becomes aware that the Dataset may or does contain personal data and shall follow the reasonable instructions issued by the University of Oxford.

3.2 The Recipient shall not:

3.2.1 use the Dataset for any purpose other than the Research, for example the Dataset may not be used for the development and/or regulatory approval of medical or clinical products, diagnostics or for commercial or for-profit purposes unless expressly included in the Data Access Application Form and subsequently approved through the application process for Data access

3.2.2 use, attempt to use or permit use of the Dataset to re-identify or contact any individual (living or deceased), community or medical institution associated with the Dataset; or

3.2.3 link, attempt to link or permit a Third Party to link the Dataset with any other data in a manner that may enable re-identification of individuals (living or deceased), communities or medical institutions associated with the Dataset; or

3.2.4 during the period of this Agreement or thereafter, disclose to any persons other than the Research Team any Confidential Information except as expressly permitted by the terms of this Agreement.

3.3 The Recipient shall:

3.3.1 ensure that each member of the Research Team who is employed by or a student at the Recipient institution will use the Dataset solely for the purposes of the Research and that each such member of the Research Team is bound to comply in full with the terms of this Agreement and any subsequent amendments, including undertakings of confidentiality equivalent to those set forth in this clause; and

3.3.2 in relation to any member of the Research Team who is employed by or a student at a Third Party, put in place a written agreement with such Third Party(s) to ensure the member of the Research Team will use the Dataset solely for the purposes of the Research and that the member of the Research Team is bound to comply in full with the terms of this Agreement and any subsequent amendments, including undertakings of confidentiality equivalent to those set forth in this clause; and

3.3.3 take all practicable steps whilst such information is in its possession or control to prevent access thereto by any person not so entitled under this Agreement; and

3.3.4 in relation to use of the Dataset allow for and contribute to audits, including inspections, conducted by or on behalf of IDDO and/or the Data Contributor, on reasonable notice and subject to appropriate confidentiality obligations.

3.4 The Recipient shall at all times be responsible for the Research Team's compliance with the obligations set out in this Agreement, including any Research Team members who are employed by or students at a Third Party.

3.5 During the Term the Recipient shall:

3.5.1 contact the Data Contributor(s) named in Schedule 1 and invite its/their participation in the planning and execution and/or publication of the Research. The Recipient may proceed without the participation of the Data Contributor if no response is received within 1 month of invitation. The structure of participation can be decided between the Recipient and each Data Contributor;

3.5.2 ensure that at all times it holds and maintains all necessary licences, permits and/or consents necessary for it to perform the Research;

3.5.3 ensure that any regulatory and/or ethics committee approvals required for use of the Dataset in the Research are obtained before the Dataset is used;

3.5.4 ensure that the Dataset is used in compliance with all Applicable Regulations, including without limitation, the UK Data Protection Act 2018, the European Convention on Human Rights and Biomedicine (1997) (including its additional protocols) and international best practices, standards and guidance, in particular relevant documents published by the

World Health Organization; (https://www.who.int/activities/ensuring-ethical-standards-and-procedures-for-research-with-human-beings);

3.5.5 observe the highest standards of ethics and integrity in the course of the Research in order to promote respect for human rights, human dignity and privacy;

3.5.6 comply with any instructions or restrictions with respect to use of the Dataset that the University of Oxford may notify to the Recipient from time to time;

3.5.7 notify the University of Oxford if it anticipates any changes to the Research and shall not implement any such change without obtaining prior written approval from the DAC; and

3.5.8 implement appropriate security measures to protect the Dataset from unauthorised access and/or disclosure. In particular the Recipient shall store the Dataset only on encrypted, access-limited, password-protected computers and/or servers. Any duplication of the Dataset must be fully documented such that all versions can be fully and permanently deleted on completion of the Term or earlier termination of this Agreement.

3.6 The Recipient warrants and undertakes to the University of Oxford that it has the right to enter into this Agreement;

3.7 The Recipient shall notify the University of Oxford as quickly as possible upon becoming aware of any unauthorised use or disclosure of, or access to, the Confidential Information and/or Dataset and the Recipient shall promptly take such action to remediate the same as IDDO and/or the DAC may reasonably require.

4. REPORTING AND INTELLECTUAL PROPERTY

4.1 The Recipient will inform the University of all Research Results produced within 1 month of publication or completion.

4.2 All Background IP is and shall remain the exclusive property of the Party owning it (or, where applicable, the Third Party from whom its right to use the Background IP has derived) and nothing in this Agreement shall operate to transfer any Background IP of one Party to the other.

4.3 The Recipient grants the University of Oxford a licence (which is irrevocable, perpetual, transferable, non-exclusive, sub-licensable and royalty free) to use and make available the Research Results for research, humanitarian, education, public health emergency response and other non-commercial purposes.

4.4 The Recipient shall use diligent efforts to make sure that the Research Results are accessible and available including taking steps to disseminate the Research Results in countries where data in the Dataset were collected.

4.5 The Recipient agrees that it will not enter into any dealing whatsoever with any other person which conflicts with this Agreement. In particular, the Recipient shall:

4.5.1 not enforce any Intellectual Property Rights it may own with respect to the Research Results against any person without the University of Oxford's prior written consent;

4.5.2 not draft or file any applications to obtain patent protection (or other similar or equivalent protection) with respect to the Research Results in any jurisdiction without the University of Oxford's prior written consent; and

4.5.3 procure that all persons to whom the Recipient licenses the Research Results enter into a binding written agreement with the Recipient under which it agrees to comply with terms materially equivalent to those set out in this Clause.

4.6 The Recipient acknowledges that the University of Oxford may reproduce the contents of approved applications and the Research Results on their websites or other media with due attribution to the Recipient.

5. PUBLICATION

5.1 The Recipient shall Publish or submit for Publication to an open-access, peer-reviewed journal, the Research Results (irrespective of the outcome of the Research) during the Term or such other period agreed between the Parties.

5.2 The Recipient shall ensure that Publications do not contain any information capable of identifying any individual (living or deceased) associated with the Dataset.

5.3 The Recipient shall take action to prevent discrimination, stigma or harm to any community identified in the Research Results.

5.4 Any Publication or presentation concerning the Dataset or the Research Results shall include citation of all digital object identifiers (DOIs) included in Schedule 1 and the following acknowledgement:

"*This research includes data obtained through a request to the Infectious Diseases Data Observatory (IDDO) https://www.iddo.org/data-sharing/accessing-data. IDDO had no role in the production of this research*". NOTE: Omit the last sentence if IDDO staff collaborate in the analysis and publication.

5.5 All Third Parties approved by the Data Access Committee to access Curated Data will be required as part of the terms of the Data Access Committee approval to invite the Contributor(s) to participate in the Proposed Research. The Contributor shall have the right but not the obligation to participate in the Proposed Research. For the avoidance of doubt, the Curated Data will be shared with the third party for the approved Proposed Research even if the Contributor declines to participate in the Proposed Research. The purpose of these requirements is to inform and include the Contributor in all use of Curated Data, insofar as the Contributor wishes to be.

6. LIMITATIONS AND EXCLUSIONS

6.1 Nothing in this Agreement excludes or limits the liability of either Party:

6.1.1 for death or personal injury caused by that Party's negligence; or

6.1.2 for fraud or fraudulent misrepresentation; or

6.1.3 to the extent that such liability cannot be limited or excluded by law.

6.2 Subject to Clause 6.1, in no event will the University of Oxford or the Data Contributor(s) be liable for any use of the Dataset by the Recipient, whether in contract, tort (including negligence or breach of statutory duty) or otherwise howsoever arising.

6.3 The Recipient acknowledges that the Dataset is provided "as is" and the University of Oxford provides the Dataset without any representation or warranty of any kind.

6.4 Subject to Clauses 6.1, 6.2 and 6.3 and insofar as any liability may not be limited or excluded by law, the total liability of the University of Oxford, whether in contract, delict or otherwise, arising in

connection with this Agreement shall not exceed ten thousand pounds sterling (£10,000) in aggregate.

7. DURATION AND TERMINATION

7.1 This Agreement, and the licences granted hereunder, shall commence on the later date of signature of the two Parties and, unless terminated earlier in accordance with this Clause, shall continue in force for the Term (as defined in the definitions).

7.2 The Recipient or the University of Oxford may terminate this Agreement at any time by notice in writing to the other Party, such notice to take effect as specified in the notice.

7.3 Without prejudice to any other rights or remedies which the University of Oxford may have, if the University of Oxford reasonably considers that the Recipient is in breach of any of its obligations under this Agreement:

7.3.1 the University of Oxford shall notify the Recipient and the Recipient shall not publish the Research Results or, to the extent already published, procure the withdrawal of the Research Results from all such publications; and

7.3.2 the University of Oxford may terminate this Agreement forthwith by notice in writing to the Recipient.

7.3.3 The University of Oxford retains the right to contact the relevant journals if the Recipient does not withdraw any published Research Results in accordance with clause 7.3.1

7.4 Upon expiry or termination of this Agreement, all licences granted to Recipient pursuant to this Agreement will automatically terminate and the Recipient shall securely destroy the Dataset and all Confidential Information and all Enriched Data to the extent that they incorporate the Dataset (and all copies thereof) in its possession or control and shall certify in writing to the University of Oxford that it has done so.

7.5 The termination or expiry of this Agreement shall not prejudice or affect any accrued rights or liabilities of any of the Parties.

7.6 Upon termination of this Agreement for any reason the provisions of Clauses 1 (*Definitions*), 2.3 to 2.5 (inclusive) (*No transfer and reservation of rights*), 3.1 to 3.3 (inclusive), 3.6 and 3.7 (*Recipient Obligations*), 4 (*Reporting and Intellectual Property*), 5 (*Publication*), 5.5 (*Limitations and Exclusions*), 7 (*Duration and Termination*), 8 (*General*), 9 (*Notices*), and 10 (*Governing Law*) shall remain in force.

8. GENERAL

8.1 This Agreement may only be amended in writing signed by duly authorised representatives of the University of Oxford and the Recipient.

8.2 The Recipient shall not assign, mortgage, charge or otherwise transfer or deal with any rights or obligations under this Agreement without the prior written consent of the University of Oxford.

8.3 No failure or delay on the part of either Party to exercise any right or remedy under this Agreement shall be construed or operate as a waiver thereof, nor shall any single or partial exercise of any right or remedy preclude the further exercise of such right or remedy.

8.4 If any provision or part of this Agreement is held to be invalid, amendments to this Agreement may be made by the addition or deletion of wording as appropriate to remove the invalid part or provision

but otherwise retain the provision and the other provisions of this Agreement to the maximum extent permissible under applicable law.

8.5 Neither Party shall act or describe itself as the agent of the other, nor shall it make or represent that it has authority to make any commitments on the other's behalf.

8.6 Each Party shall at all times comply with all applicable laws, statutes, regulations and codes relating to anti-bribery and corruption including the UK Bribery Act 2010 (as may be amended from time to time) and shall have and maintain appropriate policies and procedures to ensure compliance with such requirements (which it shall enforce where appropriate). Each Party shall immediately notify the other Party of any demand for any undue financial or other advantage of any kind received by it in connection with the subject matter of this Agreement.

8.7 This Agreement, including its schedules, sets out the entire agreement between the Parties relating to its subject matter and supersedes all prior oral or written agreements, arrangements or understandings between them relating to such subject matter. The Parties acknowledge that they are not relying on any representation, agreement, term or condition which is not set out in this Agreement.

9. NOTICES

9.1 All notices to be given and other documentation to be sent under the terms of this Agreement may be delivered personally or via email to the following:

9.1.1 in the case of IDDO: info@iddo.org

9.1.2 in the case of the Recipient: the email specified on the signature page of this document

9.2 Notices sent as above shall be deemed to have been received: if delivered personally, when left at the address noted at the start of this Agreement (or such other address as may be notified to the other party in writing from time to time); or if sent by email, on the date the confirmation copy was deemed to have been received.

10. GOVERNING LAW

The validity, construction and performance of this Agreement, and any contractual and non-contractual claims arising hereunder, shall be governed by English law and shall be subject to the exclusive jurisdiction of the English courts to which the Parties hereby submit.

EXECUTED

For and on behalf of

THE CHANCELLOR MASTERS AND SCHOLARS OF THE UNIVERSITY OF OXFORD

Signed: DocuSigned by: Emily Lloyd B38D24A38F84415...

Print name: Dr Emily Lloyd

Title: Research Contracts Lead

Date: 05 February 2024

For and on behalf of

WITS HEALTH CONSORTIUM (PTY) LTD

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

Signed:

Print name: Jean du Randt

Title: Chief Financial Officer

Date: 26 Jan 2024

Acknowledged by

MATTHEW CHERSICH

Signed: Print name: Matthew Chersich Title: Research Professor Date: 01 February 2024

Email address of Recipient for the purpose of Notices

Email: (ceo@witshealth.co.za)

SCHEDULE 1

DATASET RELEASE COVER PAGE

W_2022_3_Chersich

Data variables detailed in the Application from the following IDDO submissions are included in this release:

IDDO Submission ID	PUBMED ID
OSWYJ	29961848
PQVMQ	26962727

- Given the important public interest findings the project could potentially yield, IDDO has agreed to share personal identifier 'Date of Birth' with the applicant. The latter, together with location data of the newborn, are essential to link to the exact temperature and other climate data on the day of delivery and weeks before.
  As a DOB is considered a relatively strong identifier which in combination with other quasi-identifiers may result in a high probability of re-identification. To counter this, far-reaching and well-thought measures to limit the privacy risks for the subjects were agreed from both parties. The procedure that the applicant has agreed to comply with is the following:

1. Recoding of pt. ID to another ID with the link retained at IDDO;
2. IDDO transfers to HEAT Centre of the dataset containing pt. ID matched with DOB;
3. The HEATCentre team links pt. ID and DOB with the climatological data and then destroys the DOB;
4. Transfer of the requested outcome variables linked with pt. ID, retaining the right to omit quasi--identifiers or other variables such as child sex, singleton/multiple, maternal age, etc.

This file is the data dictionary to accompany the dataset:

IDDO SDTM Data Dictionary_v4.0_2023-05-16.xlsx

IDDO Wiki: https://wiki.iddo.org/

The organisation(s) or individual(s) listed below contributed the data in this dataset to the IDDO Data Platform. All contributors must be acknowledged or, if appropriate, included in the authorship in any Publication(s). The organisations whose contact information has been provided must be invited to participate in the Research:

Institution Name	Study ID	Contact Name	Contact Email
MRC Gambia	PQVMQ	Umberto D'Alessandro (PREGACT Study Group)	udalessandro@mrc.gm
LSHTM	OSWYJ	Henk Schallig (COSMIC Consortium)	h.d.schallig@amsterdamumc.nl

Please ensure that any Publication or presentation concerning the Dataset or the Research Results shall include citation of the digital object identifiers (DOIs) listed above (if any) and the following acknowledgement:

"*This research includes data obtained through a request to the Infectious Diseases Data Observatory (IDDO) https://www.iddo.org/data-sharing/accessing-data. IDDO had no role in the production of this research*".
NOTE: Omit the last sentence if IDDO staff collaborate in the analysis and publication.

If you have questions about this dataset, please contact curation@iddo.org.

SCHEDULE 2
DAC APPROVED DATA ACCESS APPLICATION

IDDO Data Access Application Form

Please review the Data Access Guidelines and the Data Transfer Agreement[1] before completing this form. Compliance with both will be required before access to data will be granted.

Please complete all sections of this form *fully* and return this form plus a brief *academic CV or webpage URL* and the *study selection (xls) file* (see below for instructions) to dataaccess@iddo.org

SECTION A: RESEARCHER / RESEARCH TEAM INFORMATION	
Lead Requestor Details	
Title (*delete as applicable*)	Professor
First name (given name)	Matthew
Surname (family name)	Chersich
Gender (*delete as applicable*)	Male
Position at employing organisation/ institution	Research Professor
ORCID ID https://orcid.org/	**0000-0002-4320-9168**
Email	mchersich@wrhi.ac.za
Telephone/Skype	+27 (0) 72 752 1123
Employing Organisation/Institution *Institution with a remit including health, research or academic pursuit, and with legal status which includes the scope to sign the **Data Transfer Agreement***[1]	
Institution Name	Wits Health Consortium (Pty) Ltd
Address	31 Princess of Wales Terrace, Parktown, Johannesburg, 2193, South Africa
Department (if applicable)	HE^{2}AT Center, Wits RHI
Please acknowledge that you have read the Data Transfer Agreement	YES

1 The ***Data Transfer Agreement*** *is a contract between the University of Oxford (on behalf of IDDO) and the recipient institution that governs the legal obligations and restrictions, as well as compliance with applicable laws and regulations, related to the* ***transfer*** *of such* ***data*** *between the parties. The named Institution will be required to sign the data transfer agreement before the release of any data by IDDO.*

Co-applicants (ALL individuals accessing data will need to be listed on this form. If this changes we will need to be notified) *Add rows as necessary*	
Name	Stanley Luchters
Title	Professor
Organisation/Institution	CeSHHAR
Name	Christopher Jack
Title	Dr.
Organisation/Institution	Climate System Analysis Group, University of Cape Town
Name	Sibusisiwe Makhanya
Title	Dr.
Organisation/Institution	IBM Research Africa
Name	Darshnika Lakhoo
Title	Dr.
Organisation/Institution	Wits Health Consortium (Pty) Ltd
Name	Lisa van Aardenne
Title	Ms
Organization/Institution	Climate System Analysis Group, University of Cape Town
Name	Peter Marsh
Title	Mr
Organization/Institution	Climate System Analysis Group, University of Cape Town
Name	Pierre Kloppers
Title	Mr
Organization/Institution	Climate System Analysis Group, University of Cape Town
Name	Nicholas Brink
Title	Dr
Organization/Institution	Wits Health Consortium (Pty) Ltd
Name	Craig Parker
Title	Mr
Organization/Institution	Wits Health Consortium (Pty) Ltd
Conflicts of interest *List details of any conflicts of interest (financial or non-financial) that exist relating to the use of the requested data by the data requestor and/or co-applicants (see e.g. ICJME http://icmje.org/recommendations/browse/roles-and-responsibilities/author-responsibilities--conflicts-of-interest.html)*	
None	
SECTION B: RESEARCH PLAN *Please complete **all** questions in this section. The information provided in this section will be used to assess the data request application*	
Title of Proposed Research	Developing data science solutions to mitigate the health impacts of climate change in Africa: the HE^{2}AT Center
Is this a re-submission of a previous application that has been reviewed by the IDDO DAC. If so please give reference number	No
Summary of Research in Lay Language (suggested ~ 100 words)	

The HEAT Center is an NIH funded data science project investigating heat-related clinical conditions across Africa in pregnant women and children under the age of 2.

Studies in Africa that have explored heat-health relationships are mostly small with limited geographical and temporal coverage. This project aims to overcome these limitations by combining individual level data from large numbers of studies across the continent with several climate datasets and applying data science methods in the analysis of the data.

Understanding and measuring the associations between heat and pregnancy outcomes will inform the development of a surveillance system that will track the excess contribution of heat exposure to maternal and infant morbidity and mortality.

Scientific Summary of Research (maximum 300 words)

The world's climate is changing rapidly, with global temperatures having risen more than 1°C since the industrial revolution, and a further 0.5°C increase is likely by 2040. Heat waves and rising temperatures have major, though underappreciated, health implications, particularly for vulnerable populations in low-income settings.

The Heat and Health African Transdisciplinary Center (HE^2AT Center) is part of an NIH funded (DS-I) data science project (https://reporter.nih.gov/search/E9ByPAqIaEOG4_jkFHF50g/project-details/10314149) with the overarching objective of developing innovative solutions to mitigate the health impacts of climate change in Africa.

In Africa, most studies investigating heat-health concerns rely on relatively small datasets with a narrow geographical and temporal range, allowing for only coarse assessments, as well as substantial risks of bias. To overcome these limitations, the Center will systematically develop a data ecosystem containing biomedical data, integrated with weather, air quality, environmental data, and other geospatial data within two existing, highly complementary data platforms (IBM-PAIRS and the University of Cape Town). Our project will implement an innovative data science approach to characterize the clinical outcomes of heat exposure in pregnant women and neonates. We plan to reuse data from cohorts and trials among pregnant women and neonates conducted across sub-Saharan Africa since the year 2000. Data from identified studies will be sourced from data repositories and data owners and integrated into a harmonized dataset. Then, analyses of relationships between heat exposure and adverse pregnancy and child outcomes will inform quantification of heat-related disease burden. Finally, taking all findings together, we will pilot a district-level climate change indicator, the first of its kind.

Summary of Research Objectives (maximum 200 words)

The **primary objective** is to assess the size and shape/nature of associations between exposure to high ambient temperatures and selected maternal and child conditions within the first two years postpartum.

Secondary objectives are to:

1. To assess the size and nature of associations between exposure to high ambient temperatures and other environmental exposures, and a range of maternal and child conditions and behaviours or practices;
2. To examine variations in the relationship between heat and health outcomes across different settings, climate zones and population groups;
3. To identity patterns of environmental exposures (temperature, humidity, pollution), including the shape of the association and potential threshold effects with respect to maternal and child health outcomes;
4. To develop a model for analysis of climate and health data that can be replicated for a range of heat-sensitive conditions;
5. To develop a collaboration between study groups and the IPD investigators

6. To transform the approach to heat-health analyses by demonstrating the advantages of big data IPD methodology over traditional isolated analyses in one time period and place.

Outcome Measures (maximum 200 words)

*Provide details of **primary and secondary** outcome measures*

Primary maternal and child health outcomes, include:
Maternal outcomes

1. Preterm delivery/birth (gestation <37 weeks with gestation measured before 28 weeks)
2. Premature rupture of membranes
3. Hypertensive disorders in pregnancy
4. Gestational Diabetes Mellitus

Neonatal and child health outcomes:

1. Stillbirth and infant deaths in first 2 years after birth
2. Birthweights, and infant growth in first 2 years after birth
3. APGAR score

Secondary outcomes include:
Maternal: Duration of labour, antepartum and postpartum haemorrhage, maternal sepsis and endometritis, caesarian section rate, postpartum maternal health conditions, adverse events, hospitalization, mental health
Newborn: Small for gestational age, congenital anomalies, asphyxia, admission to neonatal intensive care units, mother-to-child transmission of HIV, infections, neonatal jaundice

Proposed methodology and statistical analysis plan (maximum 400 words)

We begin with the systematic identification, acquisition and management of existing high quality cohort studies and trials among pregnant women and neonates across sub-Saharan Africa. This is being done in three ways:

1. Studies were identified through a systematic review that was conducted of all literature published between 2000 and 2020 on pregnant women in sub-Saharan Africa (PROSPERO 2020 CRD42020214637, https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020214637 and PROSPERO 2018 CRD42018118113, https://www.crd.york.ac.uk/prospero/display record.php?ID=CRD42018118113
2. A search through data repositories such as clinicalTrials.org, NICHD-DASH, BMGKi to identify studies that are stored in these repositories and/or may not have been published.
3. Principal Investigators will also be approached to identify other eligible studies particularly unpublished studies.

The datasets will be transferred to a secure server following data transfer agreements and ethical approvals. A codebook will be designed to guide the harmonisation process where relevant variables from each dataset will be recoded, if necessary, to produce one harmonized dataset. Partners on the HE^{2}AT Centre will be able to access the dataset through the secure server using a password to perform analyses.
Using the climate datasets from the IBM-PAIRS and University of Cape Town data platforms, we will apply classical time series statistical approaches to test a range of pre-specified hypotheses

based on plausible physiological pathways. We will also test the hypothesis using a range of machine learning methods, such as the gradient boosted trees, multi-level clustering, and spatiotemporal filtering approaches. The non-linear and spatial Principal Component Analysis approaches will be beneficial in the engineering of features or covariates to be tested for significance and size of effects.

Analyses will identify which sub-groups of pregnant women are most-at-risk, and which confluence of heat, socio-demographics and other environmental factors (e.g., air pollution) have significant effects on the outcomes.

Ethics (maximum 300 words)

Provide details of any ethical considerations relating to the research proposal. Is Ethics Committee or Institutional Review Board approval required by your institution to undertake this research? Have you applied or been granted ethical approval to undertake this research? If no Ethics Committee or IRB approval is required, please explain why.

This research will be carried out in accordance with International Good Clinical Practices, Declaration of Helsinki, ICH and local regulatory authorities' guidelines. Data management will adhere to ethical and legal guidelines in accordance with POPIA, other countries protection of information acts and guidelines set out by the Ethics, Legal and Social Implications component of DS-I Africa. All staff involved in this study, e.g., data managers, researchers and students will receive appropriate information on research ethics emphasizing the importance of confidentiality.

While this study is a secondary data analysis with little risk of harm, there are certain ethical considerations to be aware of. To meet the objectives of this study, we require some potentially identifying data that pertain to location and date of birth of the participants. In response, we will ensure that data is stored in a secure server, access to investigators is controlled and that the data is de-identified using encrypting algorithms and other appropriate methods.

To help us identify and address any other potential issues, the project is working with lawyers specialising in Ethical, Legal and Social Implications of research (NIH ELSI) as well as with the legal departments at Wits Health Consortium and other partner institutions.

Ethical approval will be sought from all relevant local regulatory authorities.

Publication and Dissemination Plan (maximum 300 words)

Provide details of timelines for publication and dissemination of research findings. Provide details of plans for authorship/acknowledgement of data contributors.

The HE^{2}AT Center will disseminate study findings and other learnings in a timely manner across our consortium, to policymakers, the scientific community, other stakeholders, and the general public to maximize its impact. Our engagement plan includes:

- Scientific publications and presentations to scientific conferences;
- Community engagement; and
- Policy engagement

Scientific articles will be published in open access journals allowing for wider reach of study findings. The study protocol will also be made available on open access to allow replication of the approach in other settings and will be registered with the appropriate registry. It is anticipated that the project will generate high quality data sufficient for at least four publications in high-impact journals. A publication plan is being developed within the consortium that will define the potential publications, authorship, and timeline for manuscript production. There is potential for data owners to be included in authorship based on ICMJE authorship guidelines.

Over the course of the project, there will be annual presentations to scientific conferences, such as the International Society for Environmental Epidemiology, the NIH biannual meetings, the EDCTP Forum, and others. Presentations also will be made upon request to meetings organized by the African Regional Office of the World Health Organization, the United Nations Environment Programme, the United Nations Development Programme, and others. The emphasis will be on promoting junior researchers to increase their confidence and skill in preparing and delivering scientific presentations.

The HE^{2}AT Center will promote the project and its findings among the communities in which the research will be conducted. Dissemination tools such as newsletters, brochures, and posters, may be distributed among the community. We will emphasize the guiding principles of Good Participatory Practice, including respect, mutual understanding, integrity, transparency, accountability, and autonomy.

Project results will be disseminated to the local, provincial, and national authorities, to inform their Climate Change Adaptation Planning. Very often these authorities do not receive sufficient technical support for the design and implementation of the types of solutions that will be developed through this project. This will be coordinated through Africa CDC.

Addressing Knowledge Gaps (maximum 300 words)

Provide details of how this research will address knowledge gaps of importance to those affected by or at risk of emerging and poverty-related diseases.

Globally, there remains significant potential for quantitative and analytical data science approaches to provide answers about the human health consequences of rising ambient temperatures. Systematically drawing on longitudinal health data across sub-Saharan Africa to advance innovations and solutions to climate variability and change on the sub-continent offers tremendous opportunities for developing paradigm shifting knowledge and solutions.

Analysis of pooled IPD, followed by meta-analysis of stratified data, is considered the 'gold standard' approach to collating and synthesizing evidence, with a considerably lower likelihood of bias than alternative methods. More broadly, the fact that initiatives to acquire data from cohorts and trials and then merge these into one large data set on an IPD platform are rare,

reflects the limited adoption of big data methods in health research to date. IPD analyses are classically applied to assess the efficacy of interventions tested in randomized trials, and our plan to do so with observational data is novel.

Testing quantitative analytical methods on the health outcomes of pregnant women, neonates and children provides critically important information about heat impacts in these priority population groups. Moreover, it is a proof of concept for an approach that could in future be replicated with other environmental exposures such as air pollution (using the same or other IPD databases), or consideration of other specific vulnerable population groups and health conditions affected by climate variability and change. The intention of the quantitative analytic approaches to be developed in this project is thus to provide a level of location and time-based detail that is relevant for informing current policy, clinical practice and guidance of public health responses to the climate crisis. Moreover, while the project will generate important information that is needed now, its full potential and that of the overarching approach will become evident as exposures to extreme temperatures and other climate change manifestations across the continent escalate in the coming years.

In short, by applying data sciences approaches to existing environmental and high-quality health outcomes data, the Center will develop and test innovative solutions for tracking heat-related conditions at a district level and for providing individualized early warnings of dangerous heat periods relevant to high-risk groups, industry and the general population.

Equity and Capacity Building (maximum 300 words)

Provide details of how this research will support equity of treatment and/or capacity building in endemic regions affected by or at risk of emerging and poverty-related diseases.

This research will support equity of treatment through community engagement at different levels. The Center has as one of its core strategies, a Teaching and Engagement portfolio whose mandate is to facilitate engagement with Community Advisory Boards to ensure activities reflect the demographics of the study population, is sensitive to the needs of each specific community, and to engage the appropriate community representatives and leadership. This will enable the Center to generate and disseminate outputs that are relevant and responsive to the needs of the community. In addition, a significant output from the study will be a pilot of a district-level climate change indicator which will help to mitigate the risks of increasingly intensive heatwaves to vulnerable populations such as pregnant women.

Capacity building will also take place through the Teaching and Engagement core by developing skills of early career researchers on the continent to enable them to further address the increasing challenges of climate change.

Funding (maximum 200 words)

Provide details of how this research will be funded/resourced.

The HE^{2}At Center is an NIH funded data science project (NIH DS-I Grant number: U54TW012083) and is currently funded for 5 years with the possibility of extended funding.

Scientific Review (maximum 200 words)

Provide details of how, if any, this application has been scientifically reviewed. This could be by your institution, a funder/donor or ethics committee.

This project was submitted as part of an NIH call for proposals on ***Harnessing Data Science for Health Discovery and Innovation in Africa*** (DS-I Africa:

In order to be awarded this highly competitive NIH grant, this study was scientifically reviewed by the NIH during an extremely rigorous proposal process. In addition, ethical approval is also being sought from the University of Witwatersrand research ethics committee and other relevant regulatory authorities at partner institutions. A research review board has been established with independent scientists with expertise in this field to advise on the scientific process and rigor of work at the HEAT Center.

SECTION C: DATA

Main Variables

*Provide a list of the **main variables** required to achieve the research objectives*

The main variables required are enrolment date, pregnancy stage at the enrolment, date of delivery and place/location of birth in addition to any pregnancy, birth, and child outcomes collected during the study.

Studies Required

Please include details of all of the requested studies in this section, but highlight clearly DAC controlled studies:

*Access the IDDO disease theme data inventories and search for datasets using PubMed ID numbers. You can download a list of datasets via the Download Selection button at the bottom left of the inventory. Please save the file with the name format **[name-date-data request.xls]** and submit the file (for internal use only) with this form.*

	WWARN Identifier	PMID	Access	Publication Title
1	OSWYJ	29961848	CC	Community-based Malaria Screening and Treatment for Pregnant Women Receiving Standard Intermittent Preventive Treatment With Sulfadoxine-Pyrimethamine: A Multicenter (The Gambia, Burkina Faso, and Benin) Cluster-randomized Controlled Trial.
2	EQHSD	27622558	CC	Scheduled Intermittent Screening with Rapid Diagnostic Tests and Treatment with Dihydroartemisinin-Piperaquine versus Intermittent Preventive Therapy with Sulfadoxine-Pyrimethamine for Malaria in

				Pregnancy in Malawi: An Open-Label Randomized Controlled Trial.
3	PQVMQ	26962727	DAC	Four Artemisinin-Based Treatments in African Pregnant Women with Malaria.
4	TINZU	26258474	CC	A Non-Inferiority, Individually Randomized Trial of Intermittent Screening and Treatment versus Intermittent Preventive Treatment in the Control of Malaria in Pregnancy.