

**THERAPEUTIC HYPOTHERMIA FOR NEONATAL HYPOXIC
ISCHAEMIC ENCEPHALOPATHY IN SUB-SAHARAN AFRICA:
A SCOPING REVIEW**

by

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Lastly, I would like to acknowledge everyone who has supported me both directly and indirectly with completing this thesis.

THESIS FORMAT

The format of the thesis is a publication-ready manuscript to be submitted for publication in The Lancet Global Health Journal.

The author guidelines for Lancet Global Health are attached as Appendix IV.

Scoping review publications in Lancet Global Health are described under the Green Section (different to systematic reviews) – this has been confirmed with the editor. Reviews should be no more than 4500 words, with a maximum of 75 references. A 150-word unstructured summary (abstract) should be included. All research papers must include a panel putting their research into context with previous work, with headings: evidence before this study (including a description of the evidence and search strategy if a review); added value of this study; and, implications of all the available evidence.

Reviews should not be limited to English language publications - in this review non-English publications would only have been excluded if a translation was not available, however, no non-English publications met selection criteria.

Lancet Global Health does not stipulate a font and spacing for manuscripts. The manuscript has been standardised to Times New Roman size 11 for the main text, with spacing 1.15.

Tables and figure legends have been standardised to Times New Roman, with font size standardised to the recommendations for supplementary tables.

AUTHOR CONTRIBUTIONS

The study was conceptualized by Alan Horn (AH). Naa Buxton-Tetteh (NBT), under supervision of Shakti Pillay (SP) and AH, wrote the study protocol, designed the data extraction forms, developed and performed the literature search, screened references at all stages, extracted data from full texts by consensus with AH, developed and filled the summary tables, and wrote the manuscript. SP independently screened references and extracted data from full texts.

Gugu Kali critically reviewed the study protocol and discussed disagreements.

All authors critically reviewed and approved the final version of the manuscript.

All authors had full access to all the data in the study and accept responsibility to submit for publication.

ETHICAL APPROVAL

The study was conducted in accordance with the principles of the declaration of Helsinki of 2013.

Since all data were collected from publicly accessible papers, an ethics waiver was granted by the Health Sciences Faculty, Human Research Ethics committee, University of Cape Town (HREC/REF: 789/2023).

In accordance with scoping review practice, the draft protocol was registered on the Open Science Framework and is accessible at https://osf.io/r374b/?view_only=142c9000e7664f2f9cef386c603df5c9

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ABSTRACT

There are divergent views regarding therapeutic hypothermia (TH) for neonatal hypoxic ischaemic encephalopathy (HIE) in low- and middle-income countries. The aim of this review was to synthesize the literature describing TH for HIE in sub-Saharan Africa by searching Pubmed, Scopus, Google Scholar, and Web of Science from 1996–2023. Thirty records were included: Three surveys, one feasibility study and 26 publications describing 21 cohorts, cooling 1420 babies in South Africa, Uganda, and Ghana. There were five studies recruiting at follow-up, five pilot studies, one randomised controlled trial, one case series, and 10 birth cohorts. Methods and design were highly variable and often inadequate. Two adequately described studies reported survival with normal/mildly abnormal outcome in 71% and 61%, and one representative study of clinic attenders showed 7% cerebral palsy in survivors. Loss to follow-up was 33–36%. Although outcomes were similar to global norms, the high loss to follow-up limits interpretation.

Keywords/MeSH terms: Neonate, newborn; hypoxia ischemia, brain; hypothermia, induced; Africa South of the Sahara; Neonatal encephalopathy.

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ABBREVIATIONS

Abn.	Abnormal
aEEG	Amplitude-integrated Electroencephalography
APPH	Acute Peri-partum Hypoxia
AS	Apgar Score
ASD	Anti-seizure drug
BAER	Brainstem auditory evoked responses
bps	Beats per minute
BSID-III	Bayley scales of infant and toddler development, third edition
BD	Base Deficit
BVM	Bag mask Ventilation
C	Clonidine
Cerebral-C	Cerebral Cooling
CFM	Cerebral Function Monitor
Chorio.	Chorioamnionitis
Clin	Clinical
CPR	Cardio-pulmonary resuscitation
Crit	Criteria
CT	Computerised Tomography
CUS	Cranial Ultrasound
CP	Cerebral Palsy
DC	Discharge
DRC	Democratic Republic of Congo
ECDC	Early Childhood Development Criteria
Fio2	Fraction of inspired oxygen
F-passive	Facilitated passive cooling
g	Gram
GA	Gestational Age
Gd	Grade
GMDS	Griffiths Mental Development Scales
GMFCS-E&R	Gross Motor Functional Classification System-Expanded and Revised
h/hly	Hour/Hourly
HELIX	Hypothermia for encephalopathy in low-income countries
HIC	High-income country
HIE	Hypoxic Ischemic Encephalopathy
HIV	Human Immunodeficiency Virus
ILCOR	International Liaison Committee on Resuscitation
IIPPV	Intubated Intermittent Positive Pressure Ventilation
IP	Intrapartum
IPPV	Intermittent Positive Pressure Ventilation
IQR	Interquartile range
JBI	Joanna Briggs Institute
LIC	Low Income Country
LMIC	Lower- and Middle-income Country
M	Morphine
min	Minute
MRI	Magnetic Resonance Imaging
MS	Moderate-Severe/Modified Sarnat
N	No
NE	Neonatal Encephalopathy
NEC	Necrotising Enterocolitis
NICU	Neonatal Intensive Care Unit
OAE	Oto-acoustic Emissions
P	Phenobarbitone
PA	Perinatal Asphyxia
PCC	Population/Concept/Context framework
PCM	Phase changing material
PPHN	Persistent Pulmonary Hypertension of the Newborn
PRISMA-ScR	Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
req	Required

RCT	Randomised Control Trials
SD	Standard Deviation
Servo-fan	Automated whole-body cooling with servo-controlled fan
Servo-gel	Servo controlled whole body gel-pack cooling
Servo-ice	Servo-controlled selective head cooling with ice packs
SSA	Sub-Saharan Africa
Sz	Seizure
Temp	Temperature
TH	Therapeutic Hypothermia
TOBY	Total Body Hypothermia for Neonatal Encephalopathy Trial
Trans	Transitional
TS	Thompson Score
U	Unknown/Unclear/Not Stated
wks	Weeks
Y	Yes

CHAPTER 1: PUBLICATION-READY MANUSCRIPT

TITLE PAGE (MANUSCRIPT)

THERAPEUTIC HYPOTHERMIA FOR NEONATAL HYPOXIC ISCHAEMIC ENCEPHALOPATHY IN SUB-SAHARAN AFRICA: A SCOPING REVIEW

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MAIN TEXT

RESEARCH IN CONTEXT

Evidence before this study

The incidence of Hypoxic ischaemic encephalopathy (HIE) in sub-Saharan Africa (SSA) is among the highest in world. The largest randomised controlled trial (RCT) of therapeutic hypothermia (TH) in LMICs, conducted in Asia, demonstrated no benefit of TH and increased mortality in contrast to recent meta-analyses showing reduced mortality, particularly in LMICs. No previous study has mapped and synthesized the literature describing TH for HIE in SSA. We searched Pubmed, Scopus, Google Scholar, and Web of Science from 1 January 1996 to 31 December 2023 for research studies, protocols, feasibility studies and surveys on term and near-term babies with HIE (population) treated with TH (concept) in SSA (context). We excluded conference proceedings, full text not available (all were available); and non-English language publications which could not be translated (none met inclusion criteria). We used the following search terms mapped for each element using truncation and Boolean operators, with adjustments to run on each database.

"infant, newborn", "Baby", "hypoxia ischemia, brain", "asphyxia neonatorum", "hypothermia, induced", "cool*", "hypothermia", "neuroprot*", "Africa South of the Sahara", "developing countries", "LMIC", "middle income", and "low income". The findings were synthesised and categorised into aspects of HIE diagnosis and TH management by tabular and narrative review.

Added value of this study

To our knowledge, this is the first scoping review of TH in SSA. We identified and synthesised a substantial body of literature describing TH in 1420 babies across South Africa, Uganda, and Ghana, but most studies were in South Africa. The surveys and feasibility studies had limited representation and applicability. We identified multiple study designs with variable recruitment ages and overlapping cohorts. The highly variable and often inadequate reporting of TH methods compromises generalisability and comparison of findings in many of the SSA studies. However, the adequately described birth cohort studies showed mortality rates comparable to global norms, and two adequately described and representative studies with follow-up data showed lower cerebral palsy (CP) rates than global meta analyses of TH, and the study with the lowest CP rate did not admit babies with severe HIE to NICU.

Implications of all the available evidence

This review demonstrates the need for standardised criteria and definitions and a need for a consensus minimum data set in TH studies. The data from the few adequate studies indicate acceptable outcomes, particularly where intervention for severe HIE was limited. Although the high loss to follow-up limits interpretation, the outcome for those who attended follow-up was better than expected. Ongoing and future studies should prioritise identifying the subset of babies who are least likely to benefit from cooling, and review outcomes of the babies with severe HIE and the babies who cannot be cooled in the first three hours of life. Future studies should be described in sufficient detail, to allow comparison with the RCTs providing the evidence-base for TH.

BACKGROUND

Hypoxic ischaemic encephalopathy (HIE) is an acquired syndrome of neonatal encephalopathy (NE), in term and near-term babies following acute peripartum hypoxia.¹ The annual global rate of HIE is estimated at 1·15 million cases (8·5 per 1000 births) with the highest incidence (14·9 per 1000 live births) in Sub-Saharan Africa (SSA).^{2,3} However, HIE studies are confounded by the use of different case definitions.⁴⁻⁶ The severity of HIE is graded as mild, moderate or severe using clinical assessments including the Sarnat grade,⁷ the modified Sarnat grade,^{8,9} and the Thompson HIE score.^{10,11} An abnormal amplitude integrated electroencephalogram (aEEG) identifies babies with moderate-encephalopathy,¹²⁻¹⁴ and a suppressed aEEG at 48 hours is strongly associated with neurodisability and mortality.¹⁵

In 2010, the International Liaison Committee on Resuscitation (ILCOR) recommended Therapeutic hypothermia (TH) for babies with moderate-severe HIE, due to associated improved outcomes.¹⁶ The recommendation was extended to resource-limited settings in 2015, if evidence-based protocols were used.¹⁷ Since the ILCOR recommendation, observational studies in South Africa reported favourable outcomes with TH.^{18,19} However, the hypothermia for encephalopathy in low income countries (HELIX) randomised controlled trial (RCT) of TH conducted in tertiary neonatal units in Asia, demonstrated no benefit of TH and increased mortality.²⁰ The authors suggested suspension of TH in lower- and middle-income countries (LMICs). However, the HELIX study findings are in contrast to two subsequent meta-analyses showing reduced mortality with TH in LMICs.^{21,22} In addition, the generalisability of the HELIX cohort is limited by the illness severity of participants, an uncertain contribution of intrapartum hypoxia,²³ and early seizure onset before TH.²⁴

Rationale

The findings of the HELIX trial cannot be extrapolated to SSA without reviewing all published research on TH with reference to outcomes, context, protocols, resources and definitions of HIE. The purpose of this study was to perform a scoping review to synthesise the literature describing the use of TH in SSA, which has not previously been done.

OBJECTIVES

The methodology was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) framework and guidelines from the Joanna Briggs Institute (JBI).²⁵⁻²⁷ We identified specific objectives and eligibility criteria by considering the Population/Concept/Context (PCC) framework. The objectives were:

1. Identify countries and facilities in SSA (context) that have used TH (concept) for babies with HIE (population);
2. Ascertain if TH was used as standard care or only in a research context (concept);
3. Describe how moderate-severe HIE is diagnosed (population);
4. Describe the characteristics of babies who receive TH and identify the criteria for TH (population);
5. Identify the number of babies from which TH data has been derived (population);
6. Describe the TH methods and management, including cooling depth and duration, temperature measurement and rewarming (concept);
7. Describe the complications due to TH (concept);
8. Describe the co-morbidities in babies receiving TH (concept);
9. Establish if neurological outcomes are reported and describe how they are measured (concept);
10. Describe the mortality in babies that received TH (concept);

11. Determine if quality of life outcomes were reported and describe the findings (concept);
12. Determine if surveys of TH practices exist and describe the methods and outcomes (concept).

METHODS

Eligibility criteria

The eligibility criteria for inclusion were based on the primary review purpose and the specific objectives. The inclusion criteria were determined referring to the PCC framework and study type (Box 1 and Box 2). Exclusion criteria were applied to the study types (Box 2).

Box 1. Eligibility Criteria Based on Study Population, Concept, and Context	
Category	Inclusion Criteria
Population	Multiple or individual human term and near-term (Gestation $\geq$ 35 weeks) babies with HIE
Concept	Any description of the feasibility, uptake, methods and effects of TH as treatment for HIE.
Context	Countries and facilities in SSA

Box 2. Eligibility Criteria Based on Types of Evidence		
	Inclusion Criteria	Exclusion Criteria
Types of Studies	- Primary research studies (randomised controlled trials, cohort studies, cross-sectional studies, and case reports) - Protocols for planned studies - Letters, opinion pieces or editorials - Surveys describing the use of TH	- Letters, opinion pieces or editorials which only refer to data from primary studies or surveys which have already been included - Conference proceedings - Dissertations - Articles that are written in non-English language that have not been professionally translated into English - Reviews which only refer to data from primary studies or surveys which have already been included - Full text not available

Search strategy and selection criteria

The search strategy was developed by all authors. The following electronic databases were searched from 1 January 1996 to 31 December 2023 – Medline (Pubmed), Scopus (includes Embase), Google Scholar, and Web of Science. The primary search strategy was developed for Medline (via PubMed) (Box 3). The search terms were derived using the PCC framework based on the primary review question. Keywords with synonyms and Medical Subject Headings (MeSH) were mapped for each element using truncation and Boolean operators. A filter was applied to include only studies with human participants. Only English or non-English publications for which a professional translation was available were included (but none were ultimately excluded on the basis of language). The electronic search was supplemented by publications known to the authors and by hand searching citations within the full text publications. The search terms were remapped and translated to run on each database. (Box 4.)

Box 3. Population, Concept, and Context (PCC) grid showing identified search terms with truncated Keywords and MeSH Terms for the PubMed search

Population	Concept	Content
• ("infant, newborn"[MeSH Terms] OR • "Baby"[Title/Abstract]) AND • ("humans"[Filter]) AND	• ("hypoxia ischaemia, brain"[MeSH Terms] OR • "asphyxia neonatorum"[MeSH Terms]) AND • ("hypothermia, induced" [MeSH Terms] OR • "cool*" [Title/Abstract] OR • "hypothermia"[Title/Abstract] OR • "neuroprotection"[MeSH Terms] OR • "neuroprot*" [Title/Abstract]) AND	• ("Africa South of the Sahara"[MeSH Terms] OR • "developing countries"[MeSH Terms] OR • "LMIC"[All Fields] OR • "middle income"[All Fields] OR • "low income"[All Fields])

Box 4: Keywords and MeSH Terms for Scopus, Google Scholar and Web of Science

Scopus	(INDEXTERMS ("infant, newborn") OR TITLE-ABS (baby) AND NOT INDEXTERMS (animal OR animals)) AND (INDEXTERMS ("hypoxia ischemia, brain" OR "asphyxia neonatorum") AND INDEXTERMS ("hypothermia, induced" OR "neuroprotection") OR TITLE-ABS ("cool*" OR "hypothermia" OR "neuroprot*")) AND (INDEXTERMS ("Africa South of the Sahara" OR "developing countries") OR ALL ("LMIC" OR "middle income" OR "low income"))
Google Scholar	((intitle:Infant) OR (intitle:Newborn) OR (intitle:Neonate) OR (intitle:Neonatal)) AND ((intitle:Encephalopathy) OR (intitle:Asphyxia)) AND ((intitle:Hypothermia) OR (intitle:Cooling) OR (intitle:Neuroprotection)) AND ("Africa" OR "income")
Web of Science	((((TS=(Infant* OR newborn* OR neonat* OR Baby OR Babies)) AND TS=(Encephalopathy OR Asphyxia OR Hypox*)) AND TS=(Hypothermia OR Cool* OR Neuroprot*)) AND TS=("Africa South of the Sahara" OR "Africa" OR "LMIC" OR "middle income" OR "low income" OR "sub saharan africa" OR "developing countries" OR "Angola" OR "Benin" OR "Botswana" OR "Burkina faso" OR "Burundi" OR "Cameroon" OR "Cape verde" OR "Central african republic" OR "Chad" OR "Comoro islands" OR "Congo" OR "Brazzaville" OR "Democratic republic of congo" OR "Cote d ivoire" OR "Djibouti" OR "Equatorial guinea" OR "Eritrea" OR "Ethiopia" OR "Gabon" OR "Gambia" OR "Ghana" OR "Guinea" OR "Guinea bissau" OR "Kenya" OR "Lesotho" OR "Liberia" OR "Madagascar" OR "Malawi" OR "Mali" OR "Mauritania" OR "Mauritius" OR "Mozambique" OR "Namibia" OR "Niger" OR "Nigeria" OR "Rwanda" OR "Sao tome e principe" OR "Senegal" OR "Seychelles" OR "Sierra Leone" OR "Somalia" OR "South Africa" OR "South Sudan" OR "Sudan" OR "Swaziland" OR "Tanzania" OR "Togo" OR "Uganda" OR "Western Sahara" OR "Zaire" OR "Zambia" OR "Zimbabwe"))

Evidence screening and selection (Selection of Sources of Evidence)

Endnote™20 was used to screen results and manage the de-duplication process. After performing a comprehensive search of each database, the references that met eligibility criteria were exported to individual folders on Endnote™20. The references from all sources were then copied into a new Endnote™ file where duplicates were removed by the automated but manually-reviewed process, and then saved as single file for independent review. Every study title and abstract were screened by reviewers AH and NBT together, and independently by SP, for inclusion, according to the inclusion criteria (first pass). The same reviewers, screened the full-text of those abstracts that met eligibility criteria, to confirm their eligibility for inclusion and formal data extraction (second pass). At each stage of screening, the number of excluded publications was recorded and the reasons for exclusion were recorded during full text review. Disagreements were resolved by consensus or in discussion with GK.

Data charting (Extraction)

A draft data-extraction sheet based on the primary research question and objectives was developed by all reviewers (Appendix I). Charting the results was an iterative process and the charting table was updated to include section titles and additional fields to represent data more clearly (Appendix II). Data were then independently extracted from all publications by reviewers NBT and SP using the updated data-extraction form. Disagreements were resolved by consensus or in discussion with AH and GK.

Data synthesis and presentation

The extracted data were categorised into location and study type and were summarised and described referring to descriptive data and frequency counts. Nine tables presented the data elements to align with the objectives (Table 1–9), and the results were reported using narrative synthesis. Consistent with PRISMA-ScR guidelines, we did not appraise the statistical methodology or risk of bias, and we did not provide summary measures with pooled results. However, the description of populations and TH methods was evaluated to determine variation, validity and potential comparison with other studies.

Ethics, registration and funding

The authors did not receive funding. Since all data were collected from publicly accessible papers, an ethics waiver was granted by the Health Sciences Faculty, Human Research Ethics committee, University of Cape Town (HREC/REF: 789/2023). The draft protocol was registered on the Open Science Framework and is accessible at https://osf.io/r374b/?view_only=142c9000e7664f2f9cef386c603df5c9

RESULTS

The publication screening and selection process is shown in the PRISMA flow diagram (figure 1). After full text review, 82 of 105 publications were excluded; 60 did not meet sufficient inclusion criteria, and 21 reviews/opinions/editorials and one dissertation referred to studies which were already included as primary publications. A total of 30 publications were included: 23 from the literature review^{18,19,28-48} and seven from hand-searches and prior knowledge.^{11,49-54} Four publications were dissertations,^{28,47,50,51} and one was a preprint.³² The characteristics of the publications describing TH are shown in table 1 (objectives 1 and 5). The characteristics and findings of the three surveys^{34,39,48} and one feasibility study³² are shown in table 2 (objective 12).

Countries, facilities and numbers of cooled babies in TH studies SSA (Objectives 1 and 5)

The 26 publications describing TH,^{11,18,19,29,30,32,33,35-38,40-47,49-54} included 23 studies of 21 cohorts with a total of 1420 cooled babies: 1305 in South Africa, 102 in Uganda, and 13 in Ghana (table 1). Cooling was provided in the NICU in 86% (18/21) of cohorts. Nine papers^{11,18,30,38,40,44,45,47,53} reported results from overlapping cohorts and studies. Six publications described three cohorts of cooled babies; Horn et al. described a sub study of cooled babies³⁸ within a larger HIE study,¹¹ the studies by Kali et al. in 2015⁴⁰ and 2016¹⁸ report different details from the same cohort; and Robertson et al. reported the protocol⁴⁴ and outcomes⁴⁵ for their pilot RCT separately. These six publications are described as three studies of cooled babies. Three other publications referred to a single cohort of cooled babies; the sub-cohorts of Ballot et al.³⁰ and Sebetseba et al.⁵³ overlapped and were included in the cohort of Simpson et al.⁴⁷ – these publications are described as three separate studies.

The publications describing TH had five cohort types: survivor study, pilot study, randomised controlled trial (RCT), case series and birth cohort study. Five papers described five studies of babies recruited at follow-up (survivor studies);^{19,28,30,41,54} three were small studies with selective sampling (two case-control studies^{28,41} and one illustrative follow-up study⁵⁴), and two were larger follow-up studies with time-based whole-cohort sampling.^{19,30} Six papers described five pilot studies of novel or adapted cooling methods in South Africa,^{35,36,49} Ghana,³³ and Uganda.^{4,45} One paper described a RCT of TH with or without morphine.⁵⁰ One paper included only two cooled babies (a case series).⁵² Thirteen papers described 11 observational studies of 10 cohorts of babies treated with TH and included from birth (birth cohort studies); 10 South African studies,^{11,18,37,38,40,42,43,47,51,53} including one retrospective case-control study, comparing outcomes between cooled and non-cooled babies with HIE,⁴⁶ and one Ugandan study.³²

Methods and outcomes of surveys and feasibility studies of TH practices (Objective 12)

The three surveys referring to TH in SSA, had diverse settings, objectives, and methods (table 2). Opinions and TH practice of South African paediatricians were surveyed in 2012.³⁹ Singla et al. surveyed global practice of TH for mild HIE in 2022, however SSA was represented by only 1/484 clinicians (0.2%), who was South African.⁴⁸ Evans et al. carried out a global survey to determine consensus opinion on algorithms describing new-born care in low-income countries (LICs), including SSA;³⁴ the diagnosis and management of HIE, including TH, was included in one algorithm – there was consensus on withholding TH in LICs. The South African survey had a low response rate of 37%; only 42% used TH but 75% had access to TH or planned to use it;³⁹ whole body hypothermia was used by 93% of those who cooled, but 37% measured an unvalidated target temperature on the abdomen skin surface and/or in the nasopharynx.

The only identified TH feasibility study, was in the Democratic Republic of Congo (DRC), in 2018 (table 2).³¹ Therapeutic hypothermia was not standard care at the time and feasibility was investigated in terms of age at presentation and assessment with the Thompson score. Almost half (57/134; 43%) of the babies who were admitted with acute peripartum hypoxia (“perinatal asphyxia”), presented within 6 hours of birth and had moderate-severe HIE, defined in the majority (42/57; 74%) by a Thompson score ≥ 7 . The hospitals did not have access to neonatal ventilation and all 57 babies died.

Diagnosis of HIE and criteria for TH in SSA studies (Objective 3 and 4)

The criteria for acute peri-partum hypoxia (APPH), HIE and TH in SSA are shown in table 3. Alternative terminology for APPH included peripartum/perinatal/intrapartum/birth asphyxia/hypoxia. The threshold Apgar scores at both 10 and 5 minutes, indicating APPH, ranged from 5–6 in most studies that reported it (11/14 (79%) at 10 minutes and 5/6 (83%) at 5 minutes). The need for intermittent positive pressure ventilation (IPPV) was a more frequent alternative APPH criteria at age ≥ 10 minutes or > 10 minutes in 84% (16/19). Abnormal pH and/or base deficit (BD) in the first 60 minutes of life was reported in 83% (19/23); the pH threshold for APPH was ≤ 7 or < 7 in all reporting studies, the BD threshold was ≥ 16 or

> 16 mmol/l in most (16/19; 80%), and ranged from 10–12 mmol/l in the other 3 studies.^{35,49,51} Only 26% (6/23) of studies required abnormal intrapartum events as further indicators of APPH.^{30,36-38,46,51}

All studies diagnosed HIE based on the presence of APPH with clinical signs of HIE according to one or more of the following assessments: Sarnat grade 44% (10/23); modified Sarnat grade 22% (5/23); and/or Thompson score 78% (18/23). Clinical seizures were alternative evidence of HIE in 35% (8/23). However, the moderate-severe HIE grade was only aligned with a threshold Thompson score in 44% (10/23); the majority (7/10; 70%); used a threshold of ≥ 10 or ≥ 11 but it ranged widely. The Thompson score was also used independently as a criterion for TH in 52% (12/23), however the threshold ranged widely and was not always the same as the score indicating moderate-severe HIE. All 23 studies required moderate-severe HIE based on one or more of the following assessments as additional or alternative criteria to the Thompson score: Sarnat grade 35% (8/23); modified Sarnat grade 22% (5/23); clinical seizures 52% (12/23); TOBY trial¹² clinical criteria 17% (4/23); and/or abnormal aEEG 22% (5/23).

Gestational age criteria for TH were stated in 96% (22/23) of studies; however, two studies used ≥ 34 weeks' GA,^{47,53} and the others varied from ≥ 36 to ≥ 37 weeks. The weight criteria for TH ranged from $\geq 1\,800$ g to $> 2\,000$ g (n=17/23; 74%). The age at TH initiation was < 6 or ≤ 6 hours in most reporting studies (13/17; 76%).

The exclusion criteria for TH studies in SSA are shown in table 4. Seven studies did not state exclusion criteria.^{29,30,32,33,42,46,53} Of the 16 studies that stated exclusion criteria; four were based on the TOBY trial;^{18,19,28,40,50} the criteria in the other twelve referred to illnesses masquerading as HIE and/or confounding the outcomes; six of these 12 studies also included conditions which TH may exacerbate.^{35-38,49,51} The severity of HIE was an exclusion criterion in two studies.^{43,47}

Procedures and standard care during TH in SSA studies (Objectives 2 and 6)

The procedures and standard care during TH in SSA are shown in table 5, and detailed methods are described in table 6. Therapeutic hypothermia was standard care in 83% (19/23) of studies. The TH methods included automated whole-body cooling with a mattress (eight studies),^{18,19,28,30,40,47,50,51,53} facilitated passive cooling (one pilot study),³³ servo-controlled selective head-cooling with ice-packs (one pilot study),⁴⁹ automated whole-body cooling with a servo-controlled fan (one pilot study),³⁵ servo-controlled whole-body gel-pack cooling (one pilot study and four birth cohort studies),^{32,36-38,51} manual cooling with cold water bottles (one pilot RCT),^{44,45} manual gel-bag cooling (one study),⁴⁶ and phase-changing material in MiraCradle Neonate Cooler (Pluss Advanced Technologies, India) (one study).⁴² Six studies that stated TH methods, did not state the temperature monitoring site,^{30,32,42,43,47,50,53} though it was implied by the method. The TH method was unclear in five studies; one had no description of method or target temperature,⁴¹ one stated “therapeutic hypothermia machine” without target temperature or duration of TH,⁴³ and three referred to “head” or “cerebral” cooling,^{29,52,54} with no further details other than target temperature of 34.5°C in one.⁵⁴

The time to target temperature from onset of TH ranged from 0.5–4 hours in the four studies reporting it (4/23; 17%).^{35-37,49} The target duration of TH was 72 hours in most (16/18; 89%) reporting studies; however, it was 48–72 hours in one pilot study where it was stopped early when encephalopathy resolved,⁴⁹ and 0.5–197 hours in one study reporting no complications.⁴⁶ The rate of rewarming ranged from ≤ 0.2 to $\leq 0.5^\circ\text{C}/\text{hour}$ (n=10/23; 44%). Fourteen studies^{18,19,28,30,32,36-38,40,42,43,47,50,51,53} described validated cooling methods, and eight of these studies^{11,18,28,32,36-38,40,50,51} including five birth cohort studies^{18,32,37,38,40,51} also described target core temperatures, NICU admission for severe HIE, and duration of cooling in keeping with ILCOR recommendations.

Management of HIE during TH was described in few studies and included; sedation and analgesia in 48% (11/23), anti-epileptic drugs in 44% (10/23), fluids in 17% (4/23), feeds in 4% (1/23), and empiric antibiotic use was only reported in one study.^{44,45} Cranial ultrasound availability was reported by 39% (9/23), eight of

whom had access to it,^{18,19,30,35,40,44,45,49,50} and availability of MRI was reported by 30% (7/23), three of whom had access to it.^{18,28,40,50}

The presence or absence of complications were reported by 35% (8/23) of studies; Five studies reported no adverse effects attributed to TH and all babies were cooled to 72 hours.^{18,36,40,46,47} Two studies stopped TH early due to complications; cooling was stopped in a pilot study at 40 hours due to deteriorating coagulopathy in one baby,³⁵ and Kruger et al. stopped cooling in 14% at 1–48 hours, due to “instability”.⁴¹ Two studies reported excessive temperature variation; high and variable incubator temperatures in the pilot study with solid ice-packs,⁴⁹ and core temperature was outside target range at $< 33.0^{\circ}\text{C}$ for $11 \pm 18\%$, and $> 34^{\circ}\text{C}$ for $71 \pm 22\%$ of the time in the pilot facilitated passive-cooling study.³³

Admission characteristics of babies who receive TH in SSA studies (Objective 4)

The admission characteristics of babies who received TH in SSA are shown in table 7. Maternal characteristics were infrequently reported: intrapartum (sentinel) events in 39% (9/23); maternal HIV in 52% (12/23); and clinical chorioamnionitis was only reported in the study where it was being researched.²⁸ Birth site and sex were reported by 52% (12/23) and 48% (11/23) respectively; four studies only included inborn babies,^{29,42,44,45,54} the inborn births in the other reporting studies ranged from 33–90%. Measured birth weight and assessed gestation statistics were reported by 78% (18/23) and 52% (12/23) respectively; averages ranged from 2880–3420 g and 37.7–40.3 weeks. The 5-minute Apgar scores were reported by 65% (14/23); averages varied from 3–5.2. Nine studies reported availability of blood gas from cord or baby in the first hour,^{18,28,35,36,38,40,42,43,46,51} ranging from 60–100% and in one study it was mandatory.⁴² Average pH was 6.96–7.24, and average BD was 11.5–19.9 mmol/l. Seven studies reported severity of HIE pre-cooling; severe HIE or suppressed aEEG was present in 11–61% and varied with assessment methods.^{32,33,35,38,50,51}

Co-morbidities of babies who receive TH in SSA studies (Objective 8)

The co-morbidities of babies who received TH in SSA are shown in table 8. Intubated intermittent positive pressure ventilation (IIPPV) was not available in four studies^{30,44,45,47,53} and it was not stated in the Ghanaian study.³³ Most of the studies reporting IIPPV (7/10; 70%), ventilated $\leq 50\%$ of babies. Treatment with inotropes was reported in 42% (8/19) of studies. Acquired infection and NEC were infrequent ($\leq 4\%$ in most), as was treated bleeding ($\leq 10\%$; two studies^{18,35,40}). Pulmonary hypertension and glucose abnormalities were variable and infrequently reported, occurring in 2–20%^{36,38,47,51} and 4–25%^{18,35,36,40,49-51} respectively.

Hospital stays, neurological outcomes, quality of life and mortality (Objectives 9, 10 and 11)

The Hospital stays and outcomes of babies treated with TH in SSA are shown in table 9. Quality of life outcomes were not specifically reported by any study. The rate of severe HIE was 14–55% in most (14/17; 82%) reporting studies. The average hospital stays, reported by eight studies,^{18,29,32,33,36,40,44,45,47,53} were 7–13 days with maximum stays of > 30 days in four studies.^{18,29,32,40,47} Only one study reported time to full cup or breast feeding.³² The most frequent neurological assessment method after discharge, was the Bayley scales of infant and toddler development, third edition (BSID-III), but six other methods were used, and one study reported hearing assessments.⁵⁰

Death before discharge or follow-up ranged from 0–33%. The five birth cohort studies that were aligned with ILCOR recommendations,^{18,32,37,38,40,51} reported mortalities of 16–32%. Only two of these studies clearly reported survival with normal/mildly abnormal outcome; 71% survival with non-suppressed aEEG at 48 hours³⁸ and 61% survival with normal/mildly abnormal outcome at 12 months, with 18% cerebral palsy (CP) in survivors, but 33% loss to follow-up.^{18,40} In their retrospective review of babies referred after discharge following TH, Mbatha et al. reported only 7% CP in survivors at 12 months, but 36% loss to follow-up. Babies were cooled in high care and those with severe HIE were not admitted to NICU, however other

methodology was in line with ILCOR recommendations.¹⁹ Similarly, the birth cohort studies that restricted TH or IIPV to babies ≥ 36 weeks' GA without severe HIE,⁴³ or restricted TH to inborn babies,⁴² had relatively low mortality rates (2–17%).

DISCUSSION

This scoping review identified thirty records, including three surveys, one feasibility study and 26 publications of 23 TH studies, that cooled 1420 babies. Only three studies were outside South Africa,^{32,33,44,45} two of which were pilot studies.^{33,44,45} Therapeutic hypothermia was standard care in most South African studies and one Ugandan study.³² There were multiple designs, recruitment ages, overlapping cohorts, and limited data beyond discharge. Apart from wide variation in the Thompson score thresholds for moderate-severe HIE, the criteria for APPH, moderate-severe HIE, and TH were largely similar to ILCOR recommendations.¹⁷ However TH methodology and morbidity reporting was highly variable and often inadequate. The birth cohort studies with TH methodology in line with ILCOR recommendations,¹⁷ had mortality and intact survival rates comparable with global norms.^{18,32,37,38,40,51} However, loss to follow-up was high and mortality rates were higher than in the birth cohort studies where TH or IIPV was restricted to near-term or term babies without severe HIE,⁴³ or TH was restricted to inborn babies only.⁴² Similarly, the CP rate was low in the survivor study where babies with severe HIE were not admitted to NICU.¹⁹

Surveys and feasibility studies

The South African survey was out-dated, but $< 50\%$ used TH and substantial non-standard temperature monitoring,³⁹ similar to more recent surveys in India,⁵⁵ and Brazil.⁵⁶ The global survey established consensus against TH in LICs,³⁴ in keeping with the findings of the feasibility study in DRC, showing high HIE mortality, high burden of disease, no access to neonatal intensive care, and substantial infrastructure challenges which limit the feasibility of TH.³¹

Diagnosis of HIE and criteria for TH

Consistency in diagnostic criteria facilitates robust comparisons and conclusions. However wide variation was present in this review. Intrapartum abnormalities were infrequent indicators of APPH, in keeping with acknowledged challenges in documenting such events.⁵ The use of blood gas criteria was hampered by lack of availability. The predominant indicators of APPH were resuscitation requirements based on Apgar score, and more frequently, IPPV ≥ 10 minutes – an approach supported by population studies of babies with HIE; one study showed strong correlation between a 5-minute Apgar score < 7 and acidosis,⁵ and another showed advanced neonatal resuscitation as the only independent early indicator of death.⁵⁷ The combined use of aEEG with any moderate signs of the modified Sarnat grade is most predictive for abnormal outcome,^{8,9} but both were infrequently used. The assessment most often used to diagnose HIE, was the Thompson Score, followed by Sarnat and modified Sarnat grades. However, the threshold Thompson score indicating moderate-severe HIE varied substantially, and often differed from the Thompson score that was used as a criterion for TH. Several SSA studies used the Thompson thresholds from the study of normothermic infants where the score was assigned after days, not hours.¹⁰ However, a Thompson score ≥ 7 at age 1–6 hours is the most predictive threshold for abnormal aEEG,¹¹ and abnormal MRI,⁵⁸ while a score of ≥ 8 misses 19% of babies with abnormal aEEG.⁵⁹

The GA, birth weight and ages at TH initiation were often in line with ILCOR¹⁷ recommendations; however, two studies commenced TH after 6 hours,^{18,40,49} and two studies included babies at ≥ 34 weeks' GA.^{47,53} There is no benefit of TH if commenced after 6 hours,⁶⁰ and no benefit for preterm babies < 36 weeks' GA.⁶¹ Exclusion criteria for TH were frequently not stated and were variable but were generally similar to those in the global RCTs showing benefit.^{16,62} However, some studies did not cool or did not ventilate babies with severe HIE,^{19,30,43,47,52,53} and some studies only included inborn babies.^{29,42,44,45,54}

These approaches are supported by improved outcomes associated with early initiation of TH,⁶³ and the increased benefit of TH with moderate HIE compared to severe HIE.^{62,64}

Procedures, management and morbidity during TH

The methodology of TH, admission characteristics and co-morbidities of cooled babies were often poorly described, with insufficient detail to determine validity of the TH method. Although there was less ventilation, inotrope use, bleeding and infection in the adequately described birth cohort studies^{18,32,37,38,40,51} compared to the HELIX study,²⁰ the low reporting rate limits interpretation.

Outcomes in cooled infants.

The CP rate in the largest survivor study of cooled babies who were referred after discharge,¹⁹ was substantially lower than rates reported in meta-analyses,^{22,62} but loss to follow-up was high. The outcomes in the birth cohort studies with adequate recruitment and methodology,^{18,32,37,38,40,51} had lower mortality rates than reported in the HELIX trial.²⁰ Similarly, the survival with normal/mildly abnormal outcome of 71% based on 48-hour aEEG,³⁸ and 61% based on BSIDIII at 12 months,^{18,40} is higher than the survival without neuro-disability in the HELIX trial and a recent global meta-analysis.^{20,22} The low mortality in birth cohort studies that restricted TH or IIPV to babies ≥ 36 weeks' GA without severe HIE,⁴³ or restricted inclusion to inborn babies only,⁴² and the low CP rate in the survivor study where babies with severe HIE were not admitted to NICU, are in keeping with previous reports of increased benefit in those settings.⁶²⁻⁶⁴

Strengths and Limitations

This review has several limitations which limit generalisability and comparison of findings. The studies had multiple different designs and methodology, including several pilot studies and studies with small convenience sample sizes. There were no large RCTs comparing TH to normothermia. The larger studies were observational with frequently variable and inadequately described methodology. Finally, the review excluded conference proceedings.

There are also several strengths. This is the first scoping review of TH in SSA. The methodology was in accordance with PRISMA-ScR.²⁶ Multiple objectives provided a framework for a comprehensive review. Four data bases were searched, including the grey literature in Google Scholar, and the search was performed on 31 December 2023, close to the time of manuscript submission.

CONCLUSION

This scoping review aimed to synthesise the literature describing TH in SSA, to inform opinions on the appropriateness of TH in SSA. We identified a substantial body of literature describing TH in SSA, but most was from South Africa. The surveys and feasibility studies had limited representation and applicability. The highly variable and often inadequate reporting of TH methods compromised generalisability and comparison of findings in most of the SSA studies. However, the adequately described birth cohort studies showed mortality rates comparable to global norms,^{18,32,37,38,40,51} and the two adequately described and representative studies with follow-up data^{18,19,40} showed lower CP rates than global meta analyses of TH – notably, the study with the lowest CP rate did not admit babies with severe HIE to NICU. Although the high loss to follow-up limits interpretation, the outcome for those who attended follow-up was better than expected.

This review demonstrates the need for standardised criteria for TH, more detailed methodology reporting and a consensus minimum data set for TH studies in SSA. The data from the few adequate studies suggest acceptable outcomes, particularly where intervention for severe HIE was limited, however interpretation is compromised by loss to follow up. Future studies should prioritise identifying babies who are least likely to benefit from cooling.

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CONTRIBUTORS

AH conceptualized the study. NBT, under supervision of SP and AH, wrote the study protocol, designed the data extraction forms, developed and performed the literature search, screened references at all stages, extracted data from full texts by consensus with AH, developed and filled the summary tables, and wrote the manuscript. SP independently screened references and extracted data from full texts. GK reviewed the study protocol and discussed disagreements.

All authors critically reviewed and approved the final version of the manuscript.

All authors had full access to all the data in the study and accept responsibility to submit for publication.

DATA SHARING STATEMENT

All data is accessible via the included publications and all summary data is included in the manuscript.

DECLARATION OF INTERESTS

Authors declare no competing interests.

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TABLES

Table 1: Characteristics of publications including cooled babies in sub-Saharan Africa.

1 st Author, year Data year(s)	Country City Level of care	Study Design Type of Cohort	Summarised aims (and sub study/overlap details)	Sample size
*Abrahams, 2018 ²⁸ Data: 2010–2014	South Africa Cape Town NICU	Retrospective case-control Survivor study	To study the relationship between placental pathology and neurological outcome in infants with NE and TH.	Cooled HIE: N = 17 Other HIE: N = 0 Non-HIE control: N = 30
Ballot, 2020 ³⁰ Data: 2013–2016	South Africa Johannesburg High care	Retrospective case-control Survivor study	To determine developmental outcomes in survivors of HIE (all grades) compared to healthy term babies. (June 2013–Dec 2016: overlaps with Sebetseba and Simpson)	Cooled HIE: N = 49 Other HIE: N = 35 Non-HIE control: N = 64
Krüger, 2019 ⁴¹ Data year unknown	South Africa Pretoria NICU	Prospective case-control Survivor study	To identify symptoms of oropharyngeal dysphagia in breastfeeding neonates with HIE on TH.	Cooled HIE: N = 28 Other HIE: N = 0 Non-HIE control: N = 30
Mbatha, 2021 ¹⁹ Data: 2013–2014	South Africa Johannesburg High care	Retrospective descriptive Survivor study	To determine the neurodevelopmental outcome in babies with HIE managed with TH outside NICU.	Cooled HIE: N = 113 Other HIE: N = 0 Non-HIE/control: N = 0
Stark, 2020 ⁵⁴ Data: 2010–2014	South Africa George NICU	Retrospective descriptive Survivor study	To describe developmental outcomes of infants with HIE who received TH at George Hospital from the ages of 3–60 months.	Cooled HIE: N = 30 Other HIE: N = 0 Non-HIE/control: N = 0
Enweronu-Laryea, 2019 ³³ Data: 2017	Ghana Accra Level unclear	Prospective descriptive Pilot study	To assess temperature response in relation to outcome during 80 h after birth in babies with NE undergoing facilitated passive cooling as standard management.	Cooled HIE: N = 13 Other HIE: N = 0 Non-HIE/control: N = 0
Horn, 2006 ⁴⁹ Data: 2000–2001	South Africa Cape Town NICU	Prospective descriptive Pilot study	To study the safety and efficacy of a simple, cost-effective method of selective head cooling with mild systemic hypothermia in new-born infants with HIE.	Cooled HIE: N = 4 Other HIE: N = 0 Non-HIE/control: N = 0
Horn, 2009 ³⁵ Data: 2006–2008	South Africa Cape Town NICU	Prospective descriptive Pilot study	To describe an inexpensive, computer-controlled prototype fan and to report the methodology and efficacy when using the fan to cool infants with HIE to 33–34°C.	Cooled HIE: N = 10 Other HIE: N = 0 Non-HIE/control: N = 0
Horn, 2010 ³⁶ Data: 2009	South Africa Cape Town NICU	Prospective descriptive Pilot study	To describe and evaluate a simple method of neuroprotective hypothermia for infants with HIE using gel-packs, a heatshield over the head and a radiant warmer to servo-control core temperature to 34°C.	Cooled HIE: N = 5 Other HIE: N = 0 Non-HIE/control: N = 0
Robertson, 2008 ⁴⁵ +2011 ⁴⁴ Data: 2007	Uganda Kampala Special care	Randomised controlled Pilot study	To determine feasibility of consent, neurological assessment, randomisation, and TH to core temperature 33–34°C for 72 h in a low-resource setting, using water bottles. (2008+2011 = same cohort)	Cooled HIE: N = 21 Control HIE: N = 15 Non-HIE: N = 0
*Kali, 2021 ⁵⁰ Data: 2012–2016	South Africa Cape Town NICU	Randomised controlled trial	To determine if TH + morphine improves intact survival at 18 months in infants with HIE compared to TH alone.	Cooled HIE: N = 45 Other HIE: N = 0 Cooled control: N = 22/45
Padayachee, 2013 ⁵² Data: 2006 – 2011	South Africa Johannesburg NICU	Retrospective descriptive Case series	To determine the rate and grade of HIE, survival to discharge and morbidity after discharge, of neonates with perinatal asphyxia.	Cooled HIE: N = 2 Other HIE: N = 345 Non-HIE: N = 103
Adams, 2022 ²⁹ Data: 2016–2018	South Africa Cape Town NICU	Retrospective descriptive Birth cohort	To determine which obstetric healthcare worker and/or system-related modifiable factors potentially contributed to adverse neurological outcome in babies with NE and TH.	Cooled HIE: N = 118 Other HIE: N = 0 Non-HIE/control: N = 0
† Damoi, 2020 ³² Data: 2016–2019	Uganda Kampala NICU	Retrospective descriptive Birth cohort	To determine short-term outcomes and factors associated with survival among new-born infants with moderate to severe HIE and TH.	Cooled HIE: N = 81 Other HIE: N = 0 Non-HIE/control: N = 0
Horn, 2012 ³⁷ Data: 2010–2011	South Africa Cape Town NICU	Retrospective descriptive Birth cohort	To describe temperature data of a cohort of infants with moderate-severe HIE, cooled using gel-packs, a heatshield over the head and a radiant warmer servo-controlling core temperature to 33–5°C.	Cooled HIE: N = 14 Other HIE: N = 0 Non-HIE/control: N = 0
Horn, 2013a ¹¹ +2013b ³⁸ Data: 2008–2009	South Africa Cape Town NICU	Prospective descriptive Birth cohort	To determine the threshold Thompson score at age 3–5 h that predicted an abnormal 6-h aEEG; To determine if a Thompson score at age 3–5 h predicts a severely abnormal aEEG at 48 h or death in cooled infants. (Sub study of Horn 2013a)	Cooled HIE: N = 41 Other HIE: N = 19 Non-HIE/control: N = 0
Kali, 2015 ⁴⁰ +2016 ¹⁸ Data: 2008–2011	South Africa Cape Town NICU	Retrospective descriptive Birth cohort	To describe the management, characteristics, clinical course, logistical challenges, and outcomes of infants treated with TH; and determine predictors of outcome at one year. (2015+2016 = same cohort)	Cooled HIE: N = 100 Other HIE: N = 0 Non-HIE/control: N = 0
*Kirabira, 2015 ⁵¹ Data: 2011–2012	South Africa Cape Town NICU	Retrospective descriptive Birth cohort	To compare abnormal outcome (mortality or severely abnormal aEEG at 48 h) before discharge between inborn and out born infants with HIE who were treated with TH.	Cooled HIE: N = 57 Other HIE: N = 0 Non-HIE/control: N = 0
Maphake, 2023 ⁴² Data: 2018–2019	South Africa Pretoria NICU	Retrospective descriptive Birth cohort	To investigate if Thompson score predicts outcome at day 7 or discharge in neonates with HIE who received TH; and to investigate correlation of Thompson score with risk factors associated with HIE.	Cooled HIE: N = 93 Other HIE: N = 0 Non-HIE/control: N = 0
Nakwa, 2023 ⁴³ Data: 2015–2019	South Africa Johannesburg NICU	Retrospective descriptive Birth cohort	To determine characteristics and mortality rate at hospital discharge in neonates with moderate-to-severe HIE from a large centre in a LMIC where TH is used as standard care.	Cooled HIE: N = 394 Other HIE: N = 198 Non-HIE: N = 264
Sebetseba, 2020 ⁵³ Data: 2013–2017	South Africa Johannesburg High care	Retrospective descriptive Birth cohort	To determine if neonates with NE received TH according to protocol. (1 Jan 2013–30 Jun 2017: overlaps with Ballot and Simpson)	Cooled HIE: N = 206 Other HIE: N = 279 Non-HIE/control: N = 0
Simbruner, 1999 ⁴⁶ Data: 1997–1998	South Africa Cape Town NICU	Retrospective case-control Birth cohort	To assess the physiological effects and adverse side-effects of induced hypothermia.	Cooled HIE: N = 21 Control HIE: N = 15 Non-HIE: N = 0
*Simpson, 2018 ⁴⁷ Data: 2013–2017	South Africa Johannesburg High care	Retrospective descriptive Birth cohort	To describe the characteristics and incidences of neonates diagnosed with PA, and HIE and HIE treated with TH. (1 Jan 2013–31 Jul 2017: overlaps with Ballot and Sebetseba)	Cooled HIE: N = 213 Other HIE: N = 314 Non-HIE: N = 112

* Dissertation; † Preprint; aEEG – amplitude integrated electro encephalography; HIE – hypoxic ischaemic encephalopathy; h – hour(s); LMIC – lower- or middle-income country; NE – neonatal encephalopathy; NICU – neonatal intensive care unit; PA – perinatal asphyxia; RCT – randomised controlled trial; TH – therapeutic hypothermia.

Table 2: Surveys and feasibility studies of therapeutic hypothermia in sub-Saharan Africa.

First Author, Year	Joolay, 2012 ³⁹	Singla, 2022 ⁴⁸	Evans, 2021 ³⁴	Biselele, 2018 ³¹
Countries	South Africa	Global (South Africa was the only SSA country)	South Africa, Zimbabwe, Malawi, Asia, Central America	Democratic Republic of Congo
Cities / Provinces	Multiple South African cities	Multiple global cities	Multiple global cities	Kinshasa
Primary aim	To determine opinions and practice of South African paediatricians (including neonatologists) regarding TH and management of moderate-severe HIE.	To determine global professional opinion and practice for the use of TH for mild HIE	To determine consensus opinion of experts in newborn care about key clinical decision algorithms to assist HCWs caring for facility-based unwell newborns in LICs: HIE was one of the four algorithms	To investigate the feasibility of providing neuroprotective treatment for NE in DRC: presentation with 6 hours and use of the TS as an inclusion criterion
Study type	Survey	Survey	Survey	Feasibility study
Study method	Web-based cross-sectional survey	Web-based cross-sectional survey	Two-step modified Delphi via skype	Observational study
Participants and sample size or setting	38% response rate (any response; 109/288) All/predominantly state: 45% (47/104) All/predominantly private: 55% (57/104) Neonatologists: 24% (25/104)	All surveyed 35 countries responded. 484 Neonatal clinicians in 35 countries: LMIC – 208 (43%); HIC – 276 (57%); SSA (South Africa) – 1 (0.2%)	Physician or neonatal nurse practitioner with > 10 years neonatal experience (at least 3 years in LICs). 22 invited; 14 completed round 1, ten in round 2. Nine from HIC; five from LICs. All had work experience in Africa.	134 babies included over 9 months in 2015: GA $\geq$ 36 weeks with signs of perinatal asphyxia in three public hospitals with no access to ventilation or blood gas analysis.
Cooling sample size	< 1 treated HIE in 3 months: 41% (43/104) 1–6 in 3 months: 22% (23/104) > 6 in 3 months: 37% (38/104)	Not applicable	Not applicable	43% (57/103) eligible for cooling and reached hospital by age 6 hours
APPH criteria	Not surveyed	96% (464) used one or more of, low AS, low pH, high BD, and/or an acute sentinel event.	Risk factors for HIE: Foetal distress; Resuscitation with BVM >5 minutes or CPR >10 minutes; and/or 5-minute AS <7	5-minute AS $\leq$ 5 or the need for resuscitation at age 10 minutes
Moderate-severe HIE clinical criteria / assessment method	Not surveyed	Modified Sarnat Grade: 62% Sarnat Grade: 21%, TS: 11%, Other method: 6%.	Perform TS if GA > 37 weeks and any risk factors or signs of HIE (Convulsions ; Coma; Hypotonia; Absent Moro; Absent Suck; Respiratory distress). Consider other causes if GA < 37 weeks.	TS $\geq$ 7 in first 6 hours in 74% (76/103), or 5-minute AS $\leq$ 5 + signs of perinatal asphyxia (signs not specified).
TH criteria	Not surveyed	Perinatal insult and at least one abnormality on the Sarnat assessment.	TH not recommended	GA $\geq$ 36 weeks + APPH + moderate-severe HIE
TH uptake	42% (43/102) use TH 33% (34/102) refer or planning to start TH	LMIC more likely to cool; $p < 0.05$ (25% (54/208) vs. HIC 16% (45/276))	Not stated	Not applicable; proposal only.
Cooling methods	Whole Body Hypothermia: 61% (26/43) Refrigerated gel packs: 37% (16/43) Surface/nasopharynx target: 28% (12/43) Selective Cerebral Hypothermia using CoolCap: 7% (3/43)	Methods not stated. LMIC more likely to start TH after age 6 hours (42% vs. 15%; $p < 0.05$) LMIC more likely to stop TH early if NE resolved (LMIC 31%; HIC 11%)	Cooling, in particular, passive cooling, was not recommended.	Planned method not described.
Cooling opinions	TH should be standard in tertiary units: 91% (93/102)	LMIC more likely to have a protocol (51% vs. 26%; $p < 0.05$)	Not recommended.	Not stated
aEEG use	40% (47/93) did not use EEG or aEEG	Used more often in LMIC (50% vs. HIC 30%; $p < 0.01$)	Not stated	Not used
Cranial ultrasound use	90% (83/93) of respondents to the question used Cranial ultrasound	Not stated	Not stated	Not used
CT/MRI use	MRI 21% (20/93); CT scan 15% (14/93)	Not stated	Not stated	Not used
Developmental assessment methods	Not surveyed	Formal assessment more likely in LMIC (94% vs. HIC 73%; $p < 0.05$).	Not stated	Not stated
Mortality	Not surveyed	Not applicable	Not applicable	All those eligible for cooling died (43%)

aEEG – amplitude integrated electro encephalography; APPH – acute peripartum hypoxia; AS – Apgar score; BD – Base deficit ; BVM – Bag valve mask; CPR – cardio-pulmonary resuscitation; CT – computerised tomography; GA – gestational age; HIC – high-income country; HIE – hypoxic ischaemic encephalopathy; LIC – low-income country; LMIC – lower or middle income country; MRI – magnetic resonance imaging; NE – neonatal encephalopathy; SSA – sub-Saharan Africa; TH – therapeutic hypothermia; TS – Thompson score.

Table 3: Criteria for acute peri-partum hypoxia, hypoxic ischaemic encephalopathy and therapeutic hypothermia in sub-Saharan Africa.

	APPH criteria: ^a resuscitation thresholds + IP events						HIE clin assessment: ^b methods + TS thresholds					TH assessment indications: ^c criteria + TS thresholds						TH maturity criteria ^d		
First author, year(s)	10-min Apgar	5-min Apgar	Age IPPV (min)	Early pH	Early BD (mmol/l)	IP event req.	Modify Sarnat Grade	Clin Sz	Sarnat	TS	TS MS-HIE	TS	Sarnat Grade MS	Modify Sarnat Grade MS	Clin Sz	TOBY Clin Crit	Abn. aEEG	GA (wks)	Wt (g)	age (h)
Survivor studies																				
Abrahams, 2018 ²⁸	≤ 6	U	≥ 10	< 7	≥ 16	N	N	N	N	Y	≥ 11	≥ 8	N	N	N	Y	N	> 36	U	≤ 6
Ballot, 2020 ³⁰	≤ 4	U	> 10	U	≥ 16	Y	N	N	Y	N	U	U	Y	N	N	N	N	> 36	> 2000	≤ 6
Krüger, 2019 ⁴¹	≤ 5	U	≥ 10	≤ 7	≥ 16	N	N	Y	N	Y	U	U	N	N	Y	N	N	≥ 37	U	< 6
Mbatha, 2021 ¹⁹	≤ 5	U	≥ 10	≤ 7	≥ 16	N	N	N	Y	N	U	U	Y	N	Y	Y	N	≥ 36	> 2000	< 6
Stark, 2020 ⁵⁴	≤ 6	U	≥ 10	U	≥ 16	N	N	Y	N	Y	≥ 11	≥ 11	N	N	Y	N	N	≥ 36	> 1800	< 6
Pilot studies																				
Enweronu-Laryea, 2019 ³³	U	≤ 5	0	U	U	N	Y	Y	N	Y	≥ 7	≥ 7	N	Y	Y	N	N	≥ 36	> 2000	U
Horn, 2006 ⁴⁹	U	≤ 6	0	U	≥ 10	N	N	N	Y	Y	U	≥ 2	N	N	Y	N	N	≥ 37	U	≤ 8
Horn, 2009 ³⁵	U	≤ 6	U	U	≥ 10	N	N	N	Y	N	U	U	Y	N	N	N	N	≥ 36	U	≤ 5
Horn, 2010 ³⁶	≤ 6	U	≥ 10	U	≥ 16	Y	N	N	Y	Y	U	U	Y	N	Y	N	Y	≥ 36	> 2000	< 6
Robertson, 2008 ⁴⁵ + 2011 ⁴⁴	U	≤ 5	0	U	U	N	N	N	Y	Y	≥ 5	≥ 5	Y	N	N	N	N	≥ 36	≥ 2000	≤ 3
TH analgesia RCTs																				
Kali, 2021 ⁵⁰	≤ 7	U	≥ 10	≤ 7	≥ 16	N	N	N	N	Y	≥ 11	≥ 11	N	N	N	Y	N	≥ 36	≥ 1800	≤ 6
Case series																				
Padayachee, 2013 ⁵²	U	≤ 5	U	U	U	N	N	N	Y	N	U	U	Y	N	N	N	N	U	> 1800	U
Birth cohort studies																				
Adams, 2022 ²⁹	U	U	≥ 10	< 7	≥ 16	N	N	Y	N	Y	≥ 10	≥ 10	N	N	Y	N	N	> 36	U	U
Damoi, 2020 ³²	U	≤ 7	≥ 10	≤ 7	≥ 16	N	N	Y	N	Y	≥ 7	≥ 7	N	N	Y	N	N	> 36	≥ 1800	U
Horn, 2012 ³⁷	≤ 6	U	≥ 10	U	≥ 16	Y	Y	N	N	Y	U	U	N	Y	Y	N	Y	≥ 36	> 2000	< 6
Horn, 2013a ¹¹ +2013b ³⁸	≤ 6	U	≥ 10	U	≥ 16	Y	Y	Y	N	Y	U	U	N	Y	Y	N	Y	≥ 36	> 2000	< 6
Kali, 2015 ⁴⁰ +2016 ¹⁸	≤ 7	U	≥ 10	≤ 7	≥ 16	N	N	N	N	Y	≥ 11	≥ 11	N	N	N	Y	N	≥ 36	≥ 1800	≤ 8-5
Kirabira, 2015 ⁵¹	≤ 6	U	≥ 10	≤ 7	> 12	Y	Y	Y	N	N	U	U	N	Y	Y	N	Y	≥ 36	≥ 1800	≤ 6
Maphake, 2023 ⁴²	U	U	U	< 7	> 16	N	Y	Y	N	Y	≥ 11	U	N	Y	Y	N	N	≥ 36	> 2000	U
Nakwa, 2023 ⁴⁵	≤ 5	U	≥ 10	< 7	≥ 16	N	N	N	Y	Y	≥ 10	≥ 10	N	N	N	N	Y	≥ 36	≥ 1800	< 6
Sebetseba, 2020 ⁵³	≤ 5	U	> 10	U	> 16	N	N	N	Y	Y	U	≥ 8	Y	N	N	N	N	≥ 34	> 2000	≤ 6
Simbruner, 1999 ⁴⁶	U	U	U	U	U	Y	N	N	N	Y	U	U	N	N	N	N	N	≥ 37	U	U
Simpson, 2018 ⁴⁷	≤ 5	U	> 10	< 7	> 16	N	N	N	Y	Y	U	≥ 7	Y	N	N	N	N	≥ 34	> 2000	≤ 6

Abbreviations: Abn – abnormal; aEEG – amplitude integrated electro encephalography; APPH – acute peripartum hypoxia; AS – Apgar score; BD – Base deficit ; BVM – Bag valve mask; Clin – clinical; CPR – cardio-pulmonary resuscitation; Crit – criteria; CT – computerised tomography; g – gram; GA – gestational age; h – hour; HIC – high-income country; HIE – hypoxic ischaemic encephalopathy; IP – intrapartum; LIC – low-income country; LMIC – lower or middle income country; min – minute; MRI – magnetic resonance imaging; MS – moderate-severe; N – no; RCT – randomised controlled trial; req – required; Sz – seizures; TH – therapeutic hypothermia; TOBY – Total Body Hypothermia for Neonatal Encephalopathy Trial; TS – Thompson score; U – unclear/unknown/not stated; wks – weeks; Y – yes.

Footnotes: ^a Criteria required to assign APPH; ^b Clinical methods used to assess HIE and TS thresholds used to indicate MS HIE; ^c Assessment criteria and TS thresholds required to qualify for TH; ^d Maturity criteria required to qualify for TH.

Table 4: Exclusion criteria for therapeutic hypothermia studies in sub-Saharan Africa.

Exclusion criteria	Author, year
Exclusion criteria not stated	^c Adams, 2022 ²⁹ ^a Ballot, 2020 ³⁰ ^c Damoi, 2020 ³² ^b Enweronu-Laryea, 2019 ³³ ^c Maphake, 2023 ⁴² ^c Sebetseba, 2020 ⁵³ ^c Simbruner, 1999 ⁴⁶
Based on TOBY trial: Surgery likely within the first three days; Abnormalities indicating poor outcome	^a Abrahams, 2018 ²⁸
Based on TOBY trial: Major congenital abnormalities requiring surgery; signs suggestive of chromosomal anomaly or brain dysgenesis.	^c Kali, 2015 ⁴⁰ +2016 ¹⁸ ^a Mbatha, 2021 ¹⁹
Based on TOBY trial: Congenital abnormalities or abnormalities requiring surgery within the first three days; Intensive care not offered because of severity of encephalopathy	^c Kali, 2021 ⁵⁰
Grade 3 HIE not routinely treated with TH; Possible causes of low Apgar scores other than perinatal asphyxia (e.g., major birth defects and chromosomal abnormalities)	^c Simpson, 2018 ⁴⁷
Major congenital abnormalities; Active bleeding; Sepsis; FiO ₂ > 0.5; Persistent hypoglycaemia or electrolyte abnormality	^b Horn, 2006 ⁴⁹
Major congenital abnormalities; Active bleeding; Sepsis; FiO ₂ > 0.8; Persistent electrolyte abnormality	^b Horn, 2009 ³⁵
Major congenital abnormalities; Active bleeding; Sepsis; FiO ₂ > 0.8; Persistent hypoglycaemia or electrolyte abnormality	^b Horn, 2010 ³⁶ ^c Horn, 2012 ³⁷
Infection at birth; Chorioamnionitis + PROM; Chromosomal syndromes; Cerebral/lethal malformations; Neonatal abstinence syndrome; Moribund; Metabolic encephalopathy; high-dose inotropes; FiO ₂ > 0.8; High Frequency Oscillation Ventilation.	^c Horn, 2013b ³⁸
Severe congenital anomaly; Congenital infection; Persistent pulmonary hypertension; Hypotension or bleeding not responding to treatment; Moribund and unlikely to benefit from cooling	^c Kirabira, 2015 ⁵¹
Meningitis; Metabolic or congenital disorders	^a Krüger, 2019 ⁴¹
No respiratory effort > 30 minutes post resuscitation (anaesthesia effects / medication excluded); Heart rate < 100 bpm 20 minutes post resuscitation; Major congenital abnormalities or chromosomal abnormalities involving brain	^c Nakwa, 2023 ⁴³
Cooling programme not commenced; Other causes of low Apgar scores; Chromosomal abnormalities; Congenital abnormalities of the central nervous system; Spinal muscular atrophy; lethal conditions	^d Padayachee, 2013 ⁵²
Apnoea; Cyanosis; asystole > 10 minutes after birth; Imminent death at assessment; Major malformations; Symptomatic infection; Out born; Parents live > 20 km away or do not speak or understand English / Luganda or do not understand the study	^b Robertson, 2008 ⁴⁵ + 2011 ⁴⁴
Major congenital abnormalities likely to affect neurological outcome; Unlikely to benefit from intensive care; non-hypoxic cause of encephalopathy; inadequate facilities or staff	^a Stark, 2020 ⁵⁴

Abbreviations: bpm – beats per minute; FiO₂ – fraction of inspired oxygen; TOBY – Total Body Hypothermia for Neonatal Encephalopathy Trial.

Footnotes: ^a Survivor study; ^b Pilot study; ^c TH analgesia RCT; ^d Case series; ^e Birth cohort study

Table 5: Standards, procedures, methods, protocols and complications during therapeutic hypothermia in sub-Saharan Africa.

First author, year(s)	TH Standard Care During Study	TH Method	Target Core Temp. °C	Core Temp. Site	Time to Target Temp. ^a (h)	Duration Cool (h)	Re-warm Rate °C/h	ILCOR Method + Target core site + °C + Duration ^b	Sedation / Analgesia ^c	ASD Protocol	Fluid Protocol	CUS done	MRI done	Empiric Antibiotics During TH	Complications Due to TH
Survivor studies															
Abrahams, 2018 ²⁸	Y	Auto-mat	33·5	Rectal	U	72	≤ 0·5	Y	M	Y	N	U	Y	U	U
Ballot, 2020 ³⁰	Y	Auto-mat	32–34·0	Rectal implied	U	72	U	N	U	N	N	Y	N	U	U
Krüger, 2019 ⁴¹	Y	U	U	U	U	72	U	N	U	N	N	N	U	U	Y
Mbatha, 2021 ¹⁹	Y	Auto-mat	33·5	Rectal	U	72	≤ 0·5	Y	U	N	N	Y	U	U	U
Stark, 2020 ⁵⁴	Y	U Selective-HC	34·5	Rectal	U	72	U	N	U	N	N	U	U	U	U
Pilot studies															
Enweronu-Laryea, 2019 ³³	Y	F-passive	33·5	Rectal	U	U	U	N	U	N	N	U	U	U	Y
Horn, 2006 ⁴⁹	N	Servo-ice	35·3	Rectal+Back ^e	0·8–4	48–72	U	N	P then M	Y	Y	Y	N	U	Y
Horn, 2009 ³⁵	N	Servo-fan	33·5	Rectal	0·6–2	72	≤ 0·5	N	P then M then C	Y	Y	Y	N	U	Y
Horn, 2010 ³⁶	Y	Servo-gel	34·0	Rectal+Back ^e	0·5–1·5	72	≤ 0·2	Y	M	Y	N	U	U	U	N
Robertson, 2008 ⁴⁵ + 2011 ⁴⁴	N	Water bottles	33·5	Rectal	U	72	≤ 0·5	N	P	Y	Y ^d	Y	U	Y	U
TH analgesia RCTs															
Kali, 2021 ⁵⁰	Y	Auto-mat	33·5	Rectal implied	U	72	≤ 0·5	Y	Routine M in 50%	N	N	Y	Y	U	U
Case series															
Padayachee, 2013 ⁵²	Trans.	U Cerebral-C	U	U	U	U	U	N	U	N	N	U	U	U	U
Birth cohort studies															
Adams, 2022 ²⁹	Y	U Head-cooling	U	U	U	U	U	N	U	N	N	U	U	U	U
Damoi, 2020 ³²	Y	Servo-gel	34·0	Implied Back ^e	U	72	≤ 0·2	Y	U	Y	N	U	U	U	U
Horn, 2012 ³⁷	Y	Servo-gel	33·5	Back ^e	≤ 3	72	≤ 0·2	Y	M	Y	N	U	U	U	U
Horn, 2013b ³⁸	Y	Servo-gel	33·5	Back ^e	U	72	≤ 0·2	Y	P then M	Y	Y	U	U	U	U
Kali, 2015 ⁴⁰ +2016 ¹⁸	Y	Auto-mat	33·5	Rectal	U	72	U	Y	M or ASD in 91%	Y	Y	Y	Y	U	N
Kirabira, 2015 ⁵¹	Y	Auto-mat or Servo-gel	33·5	Rectal or Back ^e	U	72	≤ 0·5	Y	U	N	N	U	U	U	U
Maphake, 2023 ⁴²	Y	PCM	U	U	U	72	U	N	U	N	N	U	U	U	U
Nakwa, 2023 ⁴⁵	Y	U TH-machine	U	U	U	U	U	N	U	N	N	U	U	U	U
Sebetseba, 2020 ⁵³	Y	Auto-mat	U	Rectal implied	U	U	U	N	M then P	N	N	Y	U	U	U
Simbruner, 1999 ⁴⁶	Y	Manual gel	U	Nasopharynx	U	0·5–197	U	N	Not routinely used	Y	N	U	U	U	N
Simpson, 2018 ⁴⁷	Y	Auto-mat	33·5	Rectal implied	U	72	U	N	U	N	N	U	N	U	N

Abbreviations: ASD – anti-seizure drug; Auto-mat – Automated whole-body cooling with mat; C – Clonidine; Cerebral-C – Cerebral cooling; CUS – cranial ultrasound;

F-passive – Facilitated passive cooling; h – hour(s); ILCOR – International Liason Committee on Resuscitation; Insul – insulated; M – morphine; Manual gel – Manual gel bag cooling; MRI – magnetic resonance imaging; N – no; P – Phenobarbitone; PCM – Phase-changing material; RCT – randomised controlled trial; servo-fan – Automated whole-body cooling with servo-controlled fan; Servo-gel – Servo-controlled whole-body gel-pack cooling; Servo-ice – Servo-controlled selective head cooling with ice packs; Temp – temperature; TH – therapeutic hypothermia; TH-machine – non-specific automated cooling machine; Trans – transitional; U – unclear/unknown/not stated; Water bottles – manual cooling with cold water bottles; Y – yes.

Footnotes: ^a Time from initiation of TH to reach target temp., publications stated as range or threshold; ^b Method, target core temp., temp. measurement site, and duration of TH stated and in line with ILCOR 2010 and 2015 guidelines; ^c description of sedation/analgesia during TH; ^d the only study to also mention feeding protocol; ^e “back” refers to insulated probe on the back between baby and mattress.

Table 6: Detailed therapeutic hypothermia methods in studies in sub-Saharan Africa

TH Method Type	TH Method Other name in text	TH Method (as described/commentary)	Author, year
Automated whole-body cooling with mat	Tecotherm TSmed200 N (Inspiration Healthcare Ltd, Leicestershire, UK)	Automated whole-body cooling and rewarming with mattress; rectal temp. monitored continuously via probe from cooling machine; target 33·5°C.	^a Abrahams, 2018 ²⁸ ^c Simpson, 2018 ⁴⁷ ^c Kali, 2015 ⁴⁰ +2016 ¹⁸ ^c Kali, 2021 ⁵⁰ ^c Kirabira, 2015 ⁵¹
	Servo-controlled cooling mattress.	No details of type of mattress provided by author. Target rectal temp. stated as 32–34°C	^a Ballot, 2020 ³⁰
	Criticoool MITRE® (Yavne, Israel)	Automated whole-body cooling and rewarming with mattress, to target rectal temp. 33·5 °C. Core (rectal) temp.: monitored continuously via probe from cooling machine	^a Mbatha, 2021 ¹⁹ ^c Sebetseba, 2020 ⁵³
	Blanketrol III (Cincinnati Sub-Zero [CSZ], Cincinnati, OH)	Automated whole-body cooling with mattress, to target rectal temp. 33·5°C. Core (rectal) temp.: monitored continuously via probe from cooling machine.	^c Kali, 2021 ⁵⁰
Automated cooling -non-specified	“Cooling Machine”	Non-specific reference to automated cooling method. Target temp. not stated.	^c Nakwa, 2023 ⁴³
Servo-controlled whole-body gel-pack cooling	Servo-controlled whole-body gel-pack cooling; warmer and core target 34 °C	Cool gel-packs at 7–10°C, applied to head and upper body and replaced hly. Core temp. (site not defined) servo-controlled to 34°C by overhead radiant warmer (<i>Servocrib, Servocare Medical Industries cc, Cape Town</i>)	^c Damoi, 2020 ³²
Servo-controlled whole-body gel-pack cooling	Servo-controlled whole-body gel-pack cooling; warmer target 34 °C; core target 33 – 34·5 °C	Cool gel-packs at 7–10°C, applied to head and upper body replaced hly to keep core temp. at 33–34·5°C. measured via insulated back temp. (confirmed with rectal temp.) and servo-controlled by overhead radiant warmer (<i>Servocrib, Servocare Medical Industries cc, Cape Town</i>) set to 34 °C. A heat shield covered the head. Measured mean rectal temp. 33·9±0·3°C; back 33·9±0·4°C	^b Horn, 2010 ³⁶
Servo-controlled whole-body gel-pack cooling	Servo-controlled whole-body gel-pack cooling; warmer and core target 33·5 °C	Cool gel-packs at 7–10°C, applied to head and upper body replaced hly to keep core temp. at 33·5 °C. measured via insulated back or rectal temp. and servo-controlled by overhead radiant warmer (<i>Servocrib, Servocare Medical Industries cc, Cape Town</i>) set to 33·5 °C. A heat shield covered the head.	^c Horn, 2012 ³⁷ ^c Horn, 2013 ³⁸ ^c Kirabira, 2015 ⁵¹
Facilitated passive cooling		Neonates dressed in nappy, nursed uncovered without overhead heater, in ambient temp. 28·3±0·7°C without fans/air-conditioning. Before study: surface temp. < 34°C, linen added. During study: Rectal (core) and axillary temp. measured every min. Target rectal temp.: 33–34°C. Core < 33·5°C - apply one blanket; < 33·2°C: apply second. Core < 33·0°C - place neonate in incubator.	^b Enweronu-Laryea, 2019 ³³
Servo-controlled selective head cooling with ice packs	Servo-controlled selective head cooling with ice packs	Frozen 12×12 cm gel-pack, covered with cloth, applied over anterior fontanelle, replaced 2–3 hly to maintain target rectal and scalp temps. Back skin temp. servo-controlled to target incubator temp. Target back temp.: 35–35·5°C. Target scalp temp.: 10–28°C	^b Horn, 2006 ⁴⁹
Automated whole-body cooling with a servo-controlled fan	Automated whole-body cooling with servo-controlled fan	Rectal temp. was simultaneously servo-controlled to target measured on low-reading radiant warmer and a servo-control fan blowing cephalo-caudally, where fan speed automatically changed proportionately to rectal temp. and the radiant warmer responded to rectal temp. by automatically increasing or decreasing power according to the set target temp. A heat shield covered the head. Target Rectal temp.: 33·4–33·7°C. Achieved Rectal temp.: 33·3–34°C	^b Horn, 2009 ³⁵
Phase-changing material	MiraCradle Neonate Cooler (Pluss Advanced Technologies, India)	Cooling with MiraCradle gel packs. No further details were stated by the author; however, this is a validated manual method of cooling involving regular replacement of solid phase changing material gel packs under the baby.	^c Maphake, 2023 ⁴²
Manual cooling with water bottles		Manual Whole-body cooling with mattress made of three water bottles filled with tepid tap water and covered in cotton sheet. Infants wore only a nappy and were naked or wrapped in cotton sheets or blankets. Core (rectal) temp. was maintained by adding or removing sheets, blankets, or water bottles. (<i>Tap water temp. was stable throughout the 24 hours and around 22–25°C</i>) Rectal, axillary, ambient and water bottle surface temps were monitored continuously. Target rectal temp.: 33–34°C.	^b Robertson, 2008 ⁴⁵ + 2011 ⁴⁴
Manual cooling gel-bags		Manual cool packs at 10°C placed around the babies’ heads to form a cap; cool packs replaced when nasopharyngeal temp. > 34·5°C. Abdominal skin servocontrolled or controlled manually to radiant heater target surface skin temp. 34–35°C. Target nasopharyngeal and surface skin: 34–35°C	^c Simbruner, 1999 ⁴⁶
Selective head or Cerebral cooling – non-specified	“Selective head cooling” or “Cerebral cooling”	Process / equipment not described. Target rectal temp. 34–35°C specified by one author, not specified by the other. The only validated method of head cooling is with Cool-Cap (<i>Olympic Medical, Seattle, WA, USA</i>) which was not mentioned.	^a Stark, 2020 ⁵⁴ ^d Padayachee, 2013 ⁵²

Abbreviations: hly – hourly; temp. temperature; TH – therapeutic hypothermia.

Footnotes: ^a Survivor study; ^b Pilot study; ^c TH analgesia RCT; ^d Case series; ^e Birth cohort study

Table 7: Admission characteristics of babies treated with therapeutic hypothermia in sub-Saharan Africa.

First author, year(s)	IP Events ^a	Mother HIV + ^a	Clin. Chorio ^a	Inborn ^a	Male ^a	Measured Birth Weight (g) ^b	Assessed Birth Gestation in weeks ^b	5-minute Apgar score ^b	Proportion With Early blood gas available	Early pH ^{b,c}	Early BD ^{b,c} mmol/l	Grade 3 HIE Precool ^d	Suppress Precool aEEG ^{a,d}
Survivor studies													
Abrahams, 2018 ²⁸	53% (9/17)	12% (2/17)	41% (7/17)	U	U	3209±406	39·5±1·5	4·7±1·3	82% (14/17)	6·96±0·18	16·7±4·2	U	U
Ballot, 2020 ³⁰	U	U	U	U	U	U	U	U	U	U	U	U	U
Krüger, 2019 ⁴¹	U	29% (8/28)	U	U	57% (16/28)	3420±450	40·3±1·7	U	U	U	U	U	U
Mbatha, 2021 ¹⁹	U	U	U	U	52% (59/113)	3129±480	U	5±1·8	U	U	U	U	U
Stark, 2020 ⁵⁴	80% (24/30)	13% (4/30)	U	100% (30/30)	50% (14/28)	3280 (range) (2320–4360)	U	≤ 5 in 71% (20/28)	U	U	U	U	U
Pilot studies													
Enweronu-Laryea, 2019 ³³	U	U	U	U	69% (9/13)	3138±463	39·7±1·7	4·9±1·7	U	U	U	Sarnat Gd 3 23% (3/13)	U
Horn, 2006 ⁴⁹	U	U	U	U	U	2730–3100	U	U	U	U	12–16·5	U	U
Horn, 2009 ³⁵	100% (10/10)	U	U	U	U	3215 (range) (2030–3925)	U	3·0 (range) (1–6)	100% (10/10)	U	17·3 (range) (13–25)	Sarnat Gd 3 40% (4/10)	50% (5/10)
Horn, 2010 ³⁶	U	U	U	U	U	3060 (range) (2700–3640)	U	5·0 (range) (3–6)	60% (3/5)	U	(range; n=3/5) 15·9–19·5	U	60% (3/5)
Robertson, 2008 ⁴⁵ + 2011 ⁴⁴	U	14% (3/21)	U	100% (21/21)	U	3300±500	38±1·5	4·7 (no SD)	U	U	U	U	U
TH analgesia RCTs													
Kali, 2021 ⁵⁰	29% (13/45)	9% (4/45)	U	47% (21/45)	64% (29/45)	To: 3172±466 M: 3263±646	T: 38·3±1·5 M: 38·9±1·5	< 5 in 33% (15/45)	U	< 7 in 51% (23/45)	U	TS ≥ 15: 16% (7/45)	U
Case series													
Padayachee, 2013 ⁵²	U	U	U	U	U	U	U	U	U	U	U	U	U
Birth cohort studies													
Adams, 2022 ²⁹	16% (19/118)	16% (20/118)	U	100% (118/118)	U	3086±576	U	U	U	U	U	U	U
Damoi, 2020 ³²	66% (53/81)	U	U	79% (64/81)	67% (54/81)	U	≥ 40: 38% (30/81)	< 5 in 29% (23/81)	U	U	U	TS ≥ 15: 11% (9/81)	U
Horn, 2012 ³⁷	U	U	U	U	U	3078 (range) (2140–3570)	38·0 (range) (36–42)	U	U	U	U	U	U
Horn, 2013b ³⁸	93% (38/41)	66% (27/38)	U	90% (37/41)	56% (23/41)	3220±407	U	4·0 (IQR) (3–5)	73% (30/41)	7·02±0·16	17·6 (range) (5·9–22·6)	MS Gd 3: 32% (13/41)	61% (25/41)
Kali, 2015 ⁴⁰ +2016 ¹⁸	13% (13/98)	21% (19/89)	U	33% (33/100)	59% (59/100)	3060 (range) (1960–5190)	39·0 (range) (35–43)	4·5 (range) (0–8)	81% (81/100)	7·03±0·15	U	U	U
Kirabira, 2015 ⁵¹	58% (33/57)	29% (16/56)	U	40% (23/57)	U	U	U	U	93% (53/57)	U	IB: 16·7±8·4 OB: 16·7±5·9	U	40% (22/55)
Maphake, 2023 ⁴²	U	19% (18/93)	U	100% (93/93)	U	U	U	U	100% (93/93)	U	U	U	U
Nakwa, 2023 ⁴⁵	U	U	U	U	U	3058±508	38·1±2·5	5 (IQR) (4–6)	100% (394/394)	7·05 (IQR) (6·90–7·16)	19·9 (IOR) (16–24)	U	U
Sebetseba, 2020 ⁵³	U	U	U	79% (163/206)	62% (127/206)	2880±660	38·3±2·3	4·8 (range) (0–8)	U	7·1±0·2	17·5±6·3	U	U
Simbruner, 1999 ⁴⁶	U	U	U	U	U	3087±488	39·4±1·8	5·2±2·3	76% (16/21)	7·24±0·18	11·5±7·2	U	U
Simpson, 2018 ⁴⁷	U	24% (50/213)	U	81% (173/213)	62% (132/213)	3071±478	38·7±1·9	U	U	U	U	U	U

Abbreviations: aEEG – amplitude integrated electro encephalography; AS – Apgar score; BD – Base deficit; Chorio – Chorioamnionitis; Clin – clinical; Gd – Grade; HIE – hypoxic ischaemic encephalopathy; HIV - human immunodeficiency virus; IP – intrapartum; IQR – interquartile range; MS – Modified Sarnat; **N** – no; RCT – randomised controlled trial; SD – standard deviation; TH – therapeutic hypothermia; U – unclear/unknown/not stated in cooled babies; **Y** – yes.

Footnotes: ^a Proportion reported; ^b statistics as reported in publications as mean±SD, median (IQR) or (range); ^c Early refers to first 60 minutes/cord;

^d Worst grade/appearance before cooling.

Table 8: Co-morbidities of babies treated with therapeutic hypothermia in sub-Saharan Africa.

First author, year(s)	IIPPV	NICU available for severe HIE	Inotropes	Acquired infection	NEC	Hypoglycaemia	Hyperglycaemia	Bleeding Treated	PPHN
Survivor studies									
Abrahams, 2018 ²⁸	59% (10/17)	Y	6% (1/17)	U	U	U	U	U	U
Ballot, 2020 ³⁰	IIPV not available	N	Inotropes not available	U	U	U	U	U	U
Krüger, 2019 ⁴¹	U	U	U	U	U	U	U	U	U
Mbatha, 2021 ¹⁹	10% (11/113)	N	U	U	U	U	U	U	U
Stark, 2020 ⁵⁴	U	U	U	U	U	U	U	U	U
Pilot studies									
Enweronu-Laryea, 2019 ³³	0%	U	U	0%	U	U	U	U	U
Horn, 2006 ⁴⁹	0%	Y	0%	0%	U	25% (1/4)	25% (1/4)	U	U
Horn, 2009 ³⁵	50% (5/10)	Y	50% (5/10)	10% (1/10)	U	20% (2/10)	U	10% (1/10)	U
Horn, 2010 ³⁶	40%	Y	40%	U	U	20%	U	U	20%
Robertson, 2008 ⁴⁵ + 2011 ⁴⁴	IIPV not available	N	IIPV not available	U	U	U	U	U	U
TH analgesia RCTs									
Kali, 2021 ³⁰	60% (27/45)	Y	22% (10/45)	U	4% (2/45)	38% (17/45)	24% (11/45)	U	U
Case series									
Padayachee, 2013 ⁵²	U	N	U	U	U	U	U	U	U
Birth cohort studies									
Adams, 2022 ²⁹	U	Y	U	U	U	U	U	U	U
Damoi, 2020 ³²	20% (16/81)	Y	U	U	U	U	U	U	U
Horn, 2012 ³⁷	U	Y	U	U	U	U	U	U	U
Horn, 2013b ³⁸	61% (25/41)	Y	34% (14/41)	2% (1/41)	U	U	U	U	7% (3/41)
Kali, 2015 ⁴⁰ +2016 ¹⁸	34% (34/100)	Y	17% (13/77)	U	1% (1/99)	4% (3/77)	10% (8/77)	8% (5/77)	U
Kirabira, 2015 ⁵¹	35% (20/57)	Y	16% (9/57)	4% (2/57)	2% (1/57)	16% (9/57)	U	U	9% (5/57)
Maphake, 2023 ⁴²	U	Y	38% (35/93)	U	U	U	U	U	U
Nakwa, 2023 ⁴⁵	U	N	U	U	U	U	U	U	U
Sebetseba, 2020 ⁵³	IIPV not available	N	IIPV not available	U	U	U	U	U	U
Simbruner, 1999 ⁴⁶	62% (13/21)	Y	U	U	U	U	U	U	U
Simpson, 2018 ⁴⁷	IIPV not available	N	IIPV not available	6% (12/213)	U	U	U	U	2% (4/213)

Abbreviations: IIPPV – intubated intermittent positive pressure ventilation; NEC – necrotising enterocolitis; PPHN – persistent pulmonary hypertension; RCT – randomised controlled trial; TH – therapeutic hypothermia; U – unclear/unknown/not stated in cooled babies

Table 9: Hospital stay, neurological and mortality outcomes of babies treated with therapeutic hypothermia in sub-Saharan Africa.

First author, year	Grade 3 HIE ^a	Duration Hospital Stay (days) ^b	Time to full cup/breast feed (days) ^b	Died Before DC or 12-month follow-up ^c	Survived to DC + non-suppressed 48-h aEEG	Assessment method at 12-months	Other or additional assessment methods used	Survived + normal/mildly abnormal at 12 months	Died or CP at 12 months	CP in survivors at 12 months	Lost to follow up 12 months ^d
Survivor studies											
Abrahams, 2018 ²⁸	18% (3/17)	U	U	0	U	BSID-III	U	44% (7/16)	56% (9/16)	44% (7/16)	6% (1/17)
Ballot, 2020 ³⁰	U	U	U	U	U	U	U	U	U	10% (5/49)	U
Krüger, 2019 ⁴¹	7% (2/28)	U	U	U	U	U	U	U	U	U	U
Mbatha, 2021 ¹⁹	10% (12/113)	U	U	U	U	GMDS	U	U	U	7% (5/72)	36% (41/113)
Stark, 2020 ⁵⁴	29% (8/28)	U	U	3% (1/30)	U	START	ECDC, GMFCS-E&R	74% (20/27)	33% (9/27)	31% (8/26)	10% (3/30)
Pilot studies											
Enweronu-Laryea, 2019 ³³	23% (3/13)	10±4·6	U	23% (3/13)	U	U	U	U	U	U	U
Horn, 2006 ⁴⁹	0	U	U	0	U	U	U	U	U	U	U
Horn, 2009 ³⁵	40% (4/10)	U	U	10% (1/10)	U	U	U	U	U	U	U
Horn, 2010 ³⁶	40% (2/5)	60% by D10 (3/5)	U	0	U	U	U	U	U	U	U
Robertson, 2008 ⁴⁵ + 2011 ⁴⁴	29% (6/21)	8±2·3	U	33% (7/21)	U	U	Modified optimality score	U	U	U	U
TH analgesia RCTs											
Kali, 2021 ⁵⁰	16% (7/45)	U	U	13% (6/45)	U	BSID-III	Amiel-Tison, OAE, BAER	71% (27/38)	32% (12/38)	16% (5/32)	16% (7/45)
Case series											
Padayachee, 2013 ³²	U	U	U	0	U	U	U	U	U	U	100% (2/2)
Birth cohort studies											
Adams, 2022 ²⁹	U	13 (mean, no SD) (range: 3–103)	U	11% (13/118)	U	U	U	U	U	U	10% (11/113)
Damoi, 2020 ³²	10% (8/81)	7 (IQR) (4–34)	6 (IQR) (5–8)	16% (13/81)	U	U	U	U	U	U	U
Horn, 2012 ³⁷	U	U	U	21% (3/14)	U	U	U	U	U	U	U
Horn, 2013b ³⁸	51% (21/41)	U	U	20% (8/41)	71% (29/41)	U	U	U	U	U	U
Kali, 2015 ⁴⁰ +2016 ¹⁸	23% (22/97)	9 (range) (5–46)	U	17% (17/100)	U	BSID-III	U	61% (41/67)	39% (26/67)	18% (9/50)	33% (33/100)
Kirabira, 2015 ⁵¹	39% (22/57)	U	U	32% (18/57)	U	U	U	U	U	U	U
Maphake, 2023 ⁴²	14% (13/93)	U	U	2% (2/93)	U	U	U	U	U	U	U
Nakwa, 2023 ⁴⁵	10% (40/394)	U	U	17% (67/394)	U	U	U	U	U	U	U
Sebetseba, 2020 ³³	U	8·1±7·8	U	U	U	U	U	U	U	U	U
Simbruner, 1999 ⁴⁶	U	U	U	19% (4/21)	U	U	U	U	U	U	U
Simpson, 2018 ⁴⁷	15% (32/213)	7 (IQR) (0–89)	U	12% (26/213)	U	U	U	U	U	U	U

Abbreviations: aEEG – amplitude integrated electro encephalography; BAER – Brainstem auditory evoked responses; BSID-III – Bayley scales of infant and toddler development, 3rd edition; CP – Cerebral Palsy; DC – discharge; ECDC – Early Childhood Developmental Criteria; Gd – Grade; GMFCS-E&R – Gross Motor Function Classification System-Expanded and Revised; h – hour; HIE – hypoxic ischaemic encephalopathy; IQR – interquartile range; OAE – oto-acoustic emissions; RCT – randomised controlled trial; SD – standard deviation; TH – therapeutic hypothermia; U – unclear/unknown/not stated for cooled babies.

Footnotes: ^a Proportion with grade 3 HIE as the highest reported grade; ^b statistics as reported in publications as mean±SD, median (IQR) or (range); ^c Proportion who died at discharge or by 12-months, latest available. ^d Proportion of infants, thought to be alive, in whom developmental outcomes were not available.

FIGURES

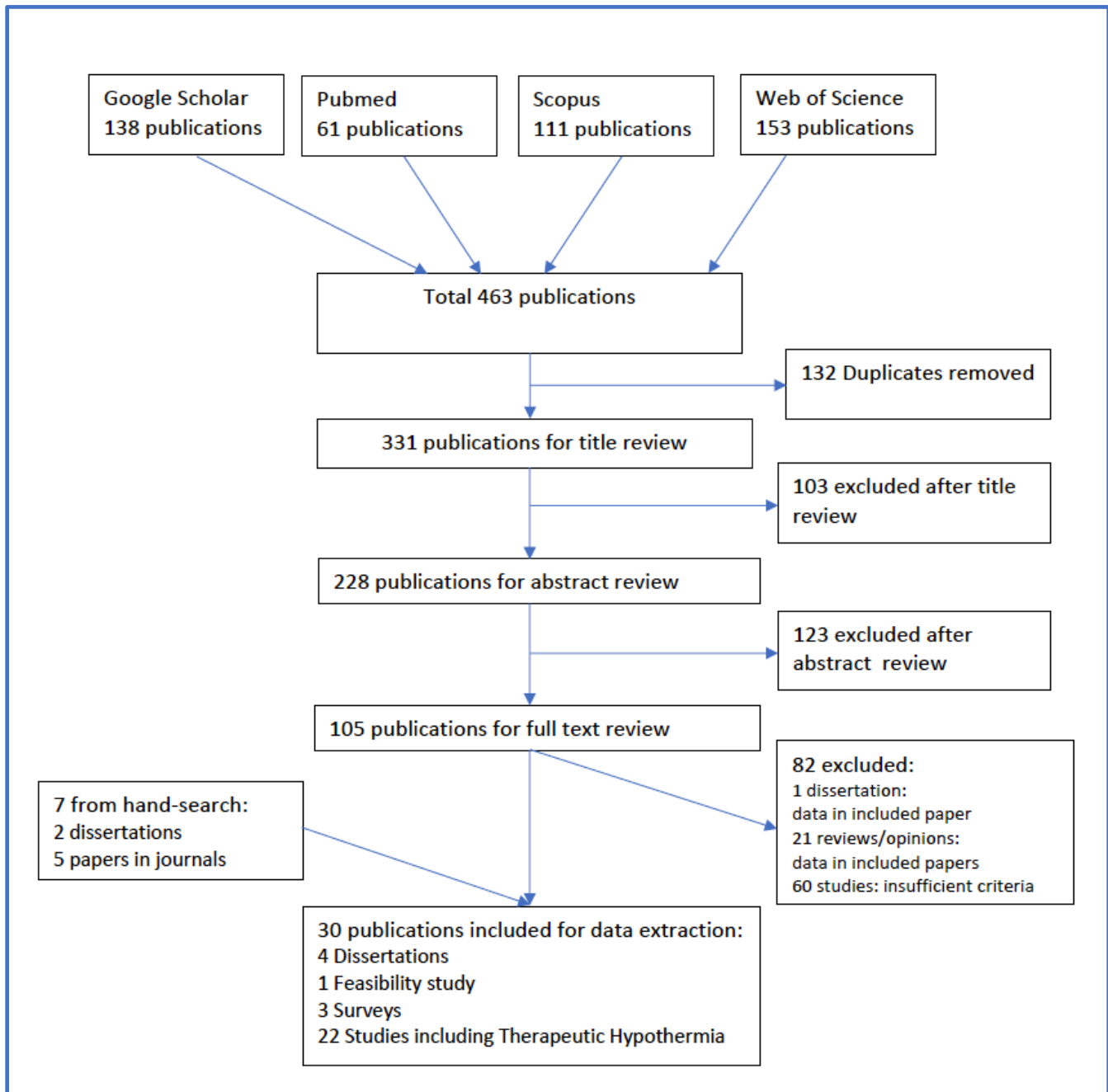


Figure 1: PRISMA flow diagram showing literature summary for studies and surveys on therapeutic hypothermia for neonatal hypoxic ischaemic encephalopathy in Sub-Saharan Africa.

APPENDICES

Appendix I: First draft data-extraction sheet

Data-extraction sheet. V1.	
Title	
Reviewer Initials	
Full Citation	
First Author	
Year of Publication	
Year(s) of Study	
Country (Published or Conducted)	
City	
Name of Facility	
Type of Facility	
Level of Care where Cooling Provided*	
Type of Study	
Primary Aim	
Other Objectives (if applicable)	
Population Inclusion Exclusion criteria:	
Diagnostic Criteria for Moderate-Severe Hypoxic Ischaemic Encephalopathy	
Neurological Assessment Method(s)	
Criteria for Cooling	
In babies who were cooled was cooling stopped prematurely? Why?	
Amplitude-integrated electroencephalography (aEEG)?	
Gestational Age (weeks)	
Birth Weight (grams)	
Percentage of Babies with Weight < 10 th Centile	
Percentage of Babies with Weight > 90 th Centile	
Apgar Score 1 minute	
Apgar Score 5 minute	
pH 1 st 60 minutes	
Base Deficit (1 st 60 minutes)	
Sample Size	
Survey Method if Applicable	
Cooling Method	
Age Cooling Started	
Cooling Duration	
Body Temperature Measurement Method and Site	
Cooling Target Temperature	
Time to Reach Target Temperature	
Rewarming Method	
Rewarming Duration	
Complications from Cooling	
Other Neuroprotective Treatments	
Anti-convulsant(s) Used for Management of Seizures	
Analgesia/Sedation Used during Cooling	
Monitoring	
Encephalopathy Grade/Score	
Percentage Ventilated	
Morbidity including Seizures	
Percentage Mortality	
Neurological Outcomes and how measured (if applicable)	
Number Lost to Follow-up (if applicable)	
Quality of Life Outcomes (if applicable)	
Is Therapeutic Hypothermia Standard Care in the Setting?	

Appendix II: Updated data-extraction sheet

SSA TH studies: Data-extraction sheet v2.	
Reviewer initials or consensus:	
Data to be extracted	Details
Study demographics	
Full citation with first 3 authors.	
Year (s) when data collected (not publication)	
Country where study conducted	
City where study conducted	
Name of facility	
Type of facility	
Level of care where cooling provided	
Type of study	
Primary Aim	
Other Objectives	
Population (participants if survey)	
Sample Size	
Proportion of cooled neonates (TH uptake if survey)	
Survey method if survey	
Criteria for hypoxia, HIE and TH	
Birth criteria for acute peripartum hypoxia	
Clinical Neurological Assessment Methods	
aEEG/EEG – use and classification	
Clinical criteria for Moderate-Severe HIE	
Inclusion Criteria for TH	
Exclusion Criteria for TH	
Neonatal characteristics at presentation - babies treated with TH	
Maternal HIV infection; (n/N) %	
Intrapartum complications/events; (n/N) %	
Chorio-amnionitis; (n/N) %	
PROM; (n/N) %	
Inborn; (n/N) %	
Male; (n/N) %	
Gestational Age (weeks)	
Birth Weight (grams)	
Birth Weight < 10 th Centile; (n/N) %	
Apgar Score 1 minute	
Apgar Score 5 minute	
Proportion with early blood gas (cord/1 st hour)	
pH 1 st 60 minutes	
Base Deficit 1 st 60 minutes	
Worst Encephalopathy Grade/Score in first 6 hours/before TH	
Worst precooling/6hrs aEEG	
Other early aEEG grade/score	
TH procedure and complications	
TH method (as much detail as provided)	
Age started	
Duration	

Body temperature measurement / site	
Target temperature / site	
Time to target temperature from TH start	
Rewarming method	
Rewarming duration	
TH stopped early for any reason ?	
Complications directly attributed to TH	
Other neuroprotective treatments	
ASD protocol	
Analgesia/sedation during TH	
Sodium Bicarbonate for metabolic acidosis	
Fluid & nutrition Protocol	
Special Monitoring	
Cranial Ultrasound Scan done?	
MRI available and done?	
Empiric antibiotics for all babies with HIE?	
Mechanical ventilation/NICU available for all? (If not, who excluded?)	
Morbidity and outcomes in cooled babies	
Proportion IIPPV; n/N (%)	
Major Morbidity:	
(Inotropes/Infection/NEC/ Hypo/per glycaemia/Bleeding/PPHN)	
Worst Encephalopathy grade	
Severely abnormal 48-hour aEEG or death	
Other aEEG outcomes	
Other clinical neurological outcomes by discharge	
Hospital stay until discharge	
Time to full cup/breast feeding	
Cranial ultrasound abnormalities	
Outcome predictors by discharge/death	
Mortality	
MRI outcomes	
Clinical neurological outcomes after discharge – when and how measured	
Number lost to clinical follow-up after discharge	
Survived and normal/mildly abnormal at 12 months	
Died or CP at 12 months	
CP in survivors at 12 months	
Quality of life outcomes	
TH standard care during study? (TH opinion if survey)	
Other Comments	

Abbreviations: aEEG – amplitude integrated electro encephalography; ASD – anti-seizure drugs; CP - cerebral palsy; HIE – hypoxic ischaemic encephalopathy; IIPV – intubated intermittent positive pressure ventilation; MRI – magnetic resonance imaging; NICU – neonatal intensive care unit; NEC – necrotising enterocolitis; PPHN – persistent pulmonary hypertension; TH – therapeutic hypothermia.

Appendix III: Ethics waiver letter



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



Room 45, E-52 Old Main Building
Groote Schuur Hospital
Observatory 7925

Email: hrec-enquiries@uct.ac.za

Website: <https://health.uct.ac.za/home/human-research-ethics>

19 October 2023

HREC/REF: 789/2023

A/Prof Alan Horn

Department of Paediatrics (Neonatology)
RmH-63, H Floor
Old Main Building
Groote Schuur Hospital
Email: alan.horn@uct.ac.za
Student: naabuxtontetteh@gmail.com

Dear A/Prof Alan Horn

PROJECT TITLE: THERAPEUTIC HYPOTHERMIA FOR NEONATAL HYPOXIC ISCHAEMIC ENCEPHALOPATHY IN SUB- SAHARAN AFRICA: A SCOPING REVIEW. (MMED DEGREE – DR NAA BUXTON-TETTEH)

Thank you for submitting your request to the Faculty of Health Sciences Human Research Ethics Committee.

The HREC note that the proposed study is a scoping review.

As the scoping review involves published literature available through publicly accessible electronic databases, research ethics review and approval is not required.

This is in accordance with Section 1.1.8 of the Department of Health's Ethics in Health Research: Principles, Processes and Structures (South African Department of Health, 2015), which states: *"Research that relies exclusively on publicly available information or accessible through legislation or regulation usually need not undergo formal ethics review. This does not mean that ethical considerations are irrelevant to the research."*

The HREC acknowledges that the student- Dr Naa Buxton-Tetteh, is also involved in this project.

Yours sincerely

PROFESSOR MARC BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

HREC REF NO. 789/2023

Appendix IV: Author Instructions

Information for Authors

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- All authors, and all contributors (including medical writers and editors), should specify their individual contributions at the end of the text
- We require that more than one author has directly accessed

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- 1 Covering letter
- 2 Manuscript including tables and panels
- 3 Figures
- 4 Author statement form (see next section)
- 5 Declaration of interests and source of funding statements (see next section)
- 6 In-press papers—one copy of each with acceptance letters
- 7 Protocols and CONSORT details for randomised controlled trials (see Articles)
- 8 We encourage disclosure of correspondence from other journals and reviewers, if previously submitted, and we might contact relevant editors of such journals
- 9 Research in context panel, for all primary research Articles

and verified the underlying data reported in the manuscript. For research articles that are the result of an academic and commercial partnership, at least one of the authors named as having accessed and verified data must be from the academic team. The contributors statement should state who those authors are.

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[Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals](#)
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[COPE Core Practices](#)
<https://publicationethics.org/core-practices>

[Author statement form](https://www.thelancet.com/for-authors/forms?section=tlgh-author-sig)
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[ICMJE Recommendations](http://www.icmje.org)
<http://www.icmje.org>

Elsevier's author guide
<https://beta.elsevier.com/about/policies-and-standards/author/dei?trial=true>

Sex and Gender Equity Research (SAGER) Guidelines
<https://researchintegrityjournal.biomedcentral.com/articles/10.1186/s41073-016-0007-6>

SAGER guidelines checklist
<https://ese.arphahub.com/article/86910/>

ICMJE COI form
<https://www.thelancet.com/for-authors/forms?section=icmje-coi>
 Joint ICMJE statement
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names and surnames of all members of the group (this is to ensure that PubMed and similar databases encode the names correctly).

Reporting sex-based and gender-based analyses

Reporting guidance

For research involving or pertaining to humans, animals, model organisms, or eukaryotic cells, investigators should integrate sex-based and gender-based analyses into their research design according to evolving funder/sponsor requirements and best practices within a field. Authors should address their research's sex and/or gender dimensions in their manuscript. In cases where they cannot, they should discuss this as a limitation to their research's generalisability. With research involving cells and model organisms, researchers should use the term "sex". With research involving humans, researchers should consider which terms best describe their data (see Definitions section below). Authors can refer to the [Sex and Gender Equity in Research \(SAGER\) Guidelines](#) and the [SAGER guidelines checklist](#). They offer systematic approaches to the use and editorial review of sex and gender information in study design, data analysis, outcome reporting, and research interpretation. However, there is no single, universally agreed-upon set of guidelines for defining sex and gender or reporting sex-based and gender-based analyses.

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In human research, the term "sex" carries multiple definitions. It often refers to an umbrella term for a set of biological attributes associated with physical and physiological features (eg, chromosomal genotype, hormonal levels, internal and external anatomy). It can also signify a sex categorisation, most often designated at birth ("sex assigned at birth") based on a newborn's visible external anatomy. The term "gender" generally refers to socially constructed roles, behaviours, and identities of women, men, and gender-diverse people that occur in a historical and cultural context, and might vary across societies and over time. Gender influences how people view themselves and each other, how they behave and interact, and how power is distributed in society. Sex and gender are often incorrectly portrayed as binary (female/male or woman/man), concordant, and static. However, these constructs exist along a spectrum that includes additional sex categorisations and gender identities, such as people who are intersex/have differences of sex development (DSD), or identify as non-binary. In any given person, sex and gender might not align, and both can change. Sex and gender are not entirely discrete concepts and their definitions continue to evolve. Biology and society influence both, and many languages do not distinguish between them. Since the terms "sex" and "gender" can be ambiguous, authors should describe the methods they use to gather and report sex-related and/or gender-related data (eg, self-report or physician-report, specific biological attributes, current sex/gender, sex assigned at birth, etc) and discuss the potential limitations of those methods. This will enhance the research's precision, rigor, and reproducibility, and avoid ambiguity or conflation of terms and the constructs to which they refer. Authors should use the term "sex assigned at birth" rather than "biological sex", "birth sex" or "natal sex" as it is more accurate and inclusive. When ascertaining gender and sex, researchers should use a two-step process: (1) ask for gender identity allowing for multiple options and (2) if relevant to the research question, ask for sex assigned at birth. In addition to this defining guidance and the

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Red section (Articles)

Articles

- *The Lancet Global Health* prioritises reports of original research that are likely to change clinical practice or thinking
- We invite submission of all clinical trials, whether phase 1, 2, 3, or 4. For phase 1 trials, we consider those of a novel substance for a novel indication, if there is a strong or unexpected beneficial or adverse response, or a novel mechanism of action
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- Reports of trials must conform to [CONSORT 2010 guidelines](#) and should be submitted with their protocols
- All reports of randomised trials should include a section entitled Randomisation and masking, within the Methods section. Please refer to *The Lancet's* [formatting guidelines for randomised trials](#)
- Cluster-randomised trials must be reported according to [CONSORT extended guidelines](#)
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WHO's International Clinical Trial Registry Platform
<http://www.who.int/ictpr/network/trds/en/index.html>

Clinical trials
<http://clinicaltrials.gov>

ICMJE recommendations
<http://icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html>

Formatting guidelines for randomised trials
<https://www.thelancet.com/for-authors/forms?section=rct>
CONSORT 2010 guidelines
<http://www.consort-statement.org/consort-2010>

CONSORT extended guidelines
<http://www.consort-statement.org/extensions/extensions/>

STARD guidelines
<http://www.equator-network.org/reporting-guidelines/stard/>

STROBE statement
<http://www.strobe-statement.org/>

STREGA guidelines
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CONSORT-AI Extension guidelines
[https://doi.org/10.1016/S2589-7500\(20\)30218-1](https://doi.org/10.1016/S2589-7500(20)30218-1)

SPRIT-AI Extension guidelines
[https://doi.org/10.1016/S2589-7500\(20\)30219-3](https://doi.org/10.1016/S2589-7500(20)30219-3)

To find reporting guidelines, see
<http://www.equator-network.org>

Human Gene Organisation
<http://www.genenames.org/>

MIAME guidelines
<http://fged.org/projects/miame/>

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<http://www.ncbi.nlm.nih.gov/geo>

- Studies of diagnostic accuracy must be reported according to [STARD guidelines](#)
- Observational studies (cohort, case-control, or cross-sectional designs) must be reported according to the [STROBE statement](#), and should be submitted with their protocols
- We encourage the registration of all observational studies on a WHO-compliant registry (see [Lancet 2010; 375: 348](#))
- Genetic association studies must be reported according to [STREGA guidelines](#)
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- Clinical trials that report interventions using artificial intelligence must be described according to the [CONSORT-AI Extension guidelines](#) and their protocols must be described according to the [SPRIT-AI Extension guidelines](#)
- To find reporting guidelines see: <http://www.equator-network.org>
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All Articles should, as relevant:

- Be up to 3500 words (4500 for randomised controlled trials) with 30 references (the word count is for the manuscript text only)
- Include an abstract (semistructured summary), with five paragraphs (Background, Methods, Findings, Interpretation, and Funding), not exceeding 250 words. Our electronic submission system will ask you to copy and paste this section at the "Submit Abstract" stage
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- Use the recommended international non-proprietary name (rINN) for drug names. Ensure that the dose, route, and frequency of administration of any drug you mention are correct
- Use gene names approved by the [Human Gene Organisation](#). Novel gene sequences should be deposited in a public database (GenBank, EMBL, or DDBJ), and the accession number provided. Authors of microarray papers should include in their submission the information recommended by the [MIAME guidelines](#). Authors should also submit their experimental details to one of the publicly available databases: [ArrayExpress](#) or [GEO](#)

- Include any necessary additional data as part of your EM submission
- All accepted Articles should include a link to the full study protocol published on the authors' institutional website (see [Lancet 2009; 373: 992](#) and [Lancet 2010; 375: 348](#))
- We encourage researchers to enrol women and ethnic groups into clinical trials of all phases, and to plan to analyse data by sex and by race

Putting research into context

- All research papers (including systematic reviews/meta-analyses) submitted to any journal in *The Lancet* family must include a panel putting their research into context with previous work in the format outlined below (see [Lancet 2014; 384: 2176-77](#), for the original rationale). This panel should not contain references. Editors will use this information at the first assessment stage and peer reviewers will be specifically asked to check the content and accuracy
- The Discussion section should contain a full description and discussion of the context. Authors are also invited to either report their own, up-to-date systematic review or cite a recent systematic review of other trials, putting their trial into context of the review

Research in context

Evidence before this study

This section should include a description of all the evidence that the authors considered before undertaking this study. Authors should briefly state: the sources (databases, journal or book reference lists, etc) searched; the criteria used to include or exclude studies (including the exact start and end dates of the search), which should not be limited to English language publications; the search terms used; the quality (risk of bias) of that evidence; and the pooled estimate derived from meta-analysis of the evidence, if appropriate.

Added value of this study

Authors should describe here how their findings add value to the existing evidence.

Implications of all the available evidence

Authors should state the implications for practice or policy and future research of their study combined with existing evidence.

Research in context panels should not contain references; key studies mentioned here should be referenced in the main text.

Data sharing

From September 21, 2020, all submitted research Articles must contain a data sharing statement, to be included at the end of the manuscript. Data sharing statements must include:

- Whether data collected for the study, including individual participant data and a data dictionary defining each field in the set, will be made available to others ("undecided" is not an acceptable answer);
- What data will be made available (deidentified participant data, participant data with identifiers, data dictionary, or other specified data set);
- Whether additional, related documents will be available (eg, study protocol, statistical analysis plan, informed consent form);

- When these data will be available (beginning and end date, or “with publication”, as applicable);
- Where the data will be made available (including complete URLs or email addresses if relevant);
- By what access criteria data will be shared (including with whom, for what types of analyses, by what mechanism – eg, with or without investigator support, after approval of a proposal, with a signed data access agreement – or any additional restrictions).

See [table](#) for examples. Clinical trials that begin enrolling participants on or after Jan 1, 2019, must include a data sharing plan in the trial’s registration. If the data sharing plan changes after registration, this should be reflected in the statement submitted and published, and updated in the registry record. [Mendeley Data](#) is a secure online repository for research data, permitting archiving of any file type and assigning a permanent and unique digital object identifier (DOI) so that the files can be easily referenced. If authors wish to share their supporting data, and have not already made alternative arrangements, a Mendeley DOI can be referred to in the data sharing statement.

Blue section (Comment, Correspondence)

Editorial

- Editorials are the voice of *The Lancet Global Health*, and are written in-house by the journal’s editorial-writing team and signed “*The Lancet Global Health*”

Comment

- This section contains Commentaries that accompany papers published in *The Lancet Global Health* or on issues of wide-reaching concern in global health. Comments linked to policy decisions are welcomed. Most Comments are commissioned, but unsolicited Comments (no more than 750 words, ten references, and one figure, panel, or small table) are also welcome. Comments may be peer reviewed
- The place to respond to something we have published is in our **Correspondence** section
- See **Conflicts of Interest** guidelines for comments

Correspondence

- Letters should be written in response to previous content published in *The Lancet Global Health*
- Letters for publication must reach us within 4 weeks of publication of the original item and should be no longer than 400 words
- Letters of general interest, unlinked to items published in the journal, can be up to 400 words long
- Correspondence letters are not usually peer reviewed, but we might invite replies from the authors of the original publication, or pass on letters to these authors
- Only one table or figure is permitted, and there should be no more than five references and five authors
- All accepted letters are edited. Proofs will be sent out to authors before publication

Corrections

- Any substantial error in any article published in *The Lancet*

Global Health should be corrected as soon as possible. Blame is not apportioned; the important thing is to set the record straight.

- The *Lancet* journals have a [policy](#) for types of errors that we do and do not correct. We will always correct any error affecting a non-proprietary drug name, dose, or unit, any numerical error in the results, or any factual error in the interpretation of results. Authorship format changes after publication to facilitate a different visualisation in MEDLINE/PubMed will not be done.

For The Lancet journals’ policy on corrections of errors see <https://www.thelancet.com/for-authors/forms?section=correction>

Green section (Reviews, Viewpoints, Health Policy, Commissions, Series)

Reviews

Reviews should be either a definitive overview of a major topic connected with global health or an update of knowledge in a somewhat narrower field of current interest. Manuscripts will be assessed in-house and those judged suitable will be peer reviewed before an editorial decision is made. Reviews should be no more than 4500 words, with a maximum of 75 references. References selected for publication should be chosen for their importance, ease of access, and for the “further reading” opportunities they provide; citations to papers published in non-peer-reviewed supplements are discouraged. In addition to references, authors should consider supplying a short list of useful websites where readers can find further information on the subject. A 150 word unstructured summary should be included. Use of up to five illustrations is encouraged to aid the reader. Complete transparency about the choice of material included is important to any Review paper. Therefore, all Reviews should include a brief section entitled “Search strategy and selection criteria” stating the sources (including databases, MeSH and free text search terms and filters, and reference lists from journals or books) of the material covered, and the criteria used to include or exclude studies. Since these papers should be comprehensive, we encourage citation of publications in non-English languages. Systematic reviews should be submitted as Original Research, not Reviews.

MENDELEY data
<https://data.mendeley.com>

Viewpoint

Viewpoints are opinion pieces that use the best evidence to develop a robust argument on a topic of immediate relevance to global health. They should have a novel and clear point to make, with the aim of provoking transformational thinking at a high level. Length guidelines are up to 2500 words and a maximum of 30 references.

Health Policy

Health Policy papers should cover developments in global health related to policy, guideline development, health systems, or economics. A mix of original research, narrative review, and advocacy can be included, as long as these elements are clearly identified. Health Policy papers are longer than Original Research Articles at up to 4500 words and a maximum of 75 references, with a 150 word unstructured summary. One or two figures or tables can be included.

Commissions

Topics for *The Lancet Global Health* Commissions are generally selected by our editors, who work with academic partners to identify the most pressing issues in science, medicine, and global health with

the aim of producing recommendations to change public policy or improve practice. Projects usually last 2–3 years, and author groups will represent a broad range of international expertise. All *The Lancet Global Health* Commissions are academic publications and are subject to the same rigorous peer review process as all other research papers published in our journals. *The Lancet Global Health* does not provide direct financial support to Commissioners for the research or writing of the reports. Funding is sought directly by authors, with oversight from our editors

Series

Series are collections of papers (usually between three and five) on a broad topic within the global health field. They are generally commissioned by the editors, but suggestions are welcome by email. We would not consider a large collection of papers on a narrow topic—eg, a single global health programme. This type of collection is better suited to a journal supplement (*The Lancet Global Health* does not publish supplements).

Formatting guidelines

Language

- Manuscripts should be submitted in English. Authors writing in Chinese, Portuguese, or Spanish may wish to use the Webshop (<http://webshop.elsevier.com/languageservices>) to provide an English translation of their manuscript for submission.

Title page

- A brief title, author name(s), preferred degree (one only), affiliation(s), and full address(es) of the authors must be included. The name and address of the corresponding author should be separately and clearly indicated with email and telephone details.

Formatting of text

- Type a single space at the end of each sentence
- Do not use bold face for emphasis within text
- We use a comma before the final “and” or “or” in a list of items
- Type decimal points midline (ie, 23·4, not 23.4). To create a midline decimal on a PC: hold down ALT key and type 0183 on the number pad, or on a Mac: ALT shift 9
- Numbers one to ten are written out in words unless they are used as a unit of measurement, except in figures and tables
- Use single hard-returns to separate paragraphs. Do not use tabs or indents to start a paragraph
- Do not use the automated features of your software, such as hyphenation, endnotes, headers, or footers (especially for references). Please use page numbering
- Guidelines on formatting tables are available in the [artwork guidelines](#)

References

- Cite references in the text sequentially in the Vancouver numbering style, as a superscripted number after any punctuation mark. For example:
“...as reported by Saito and colleagues.¹⁵”
- Two references are cited separated by a comma, with no space. Three or more consecutive references are given as a range with an

en rule. To create an en rule on a PC: hold down CTRL key and minus sign on the number pad, or on a Mac: ALT hyphen

- References in tables, figures, and panels should be in numerical order according to where the item is cited in the text
- Here is an example for a journal reference (note the use of tab, bold, italic, and the en rule or “long” hyphen):
“15[tab]Saito N, Ebara S, Ohotsuka K, Kumeta J, Takaoka K. Natural history of scoliosis in spastic cerebral palsy. *Lancet* 1998; **351**: 1687–[en rule]92.”
- Give any subpart to the title of the article
- If there are six authors or fewer, give all six in the form: surname space initials comma
- If there are seven or more give the first three in the same way, followed by et al
- For a book, give any editors and the publisher, the city of publication, and year of publication
- For a chapter or section of a book, also give the authors and title of the section, and the page numbers
- For online material, please cite the URL, together with the date you accessed the website
- Online journal articles can be cited using the DOI number
- References that are in press can be cited in the reference list with “(in press)” added after the journal name
- For personal communications and unpublished work, please cite in-text rather than in the reference list in the format “(unpublished)” or “(Smith R, unpublished)” if it is your own observation, or “(Jones E, institution, personal communication)” if it is someone else’s observation
- Do not put references in the Summary or Research in context and Search strategy and selection criteria panels
- If preprints are central to your work or cover crucial developments in the topic(s) covered in your paper, but are not yet formally published, these may be referenced. Preprints should be clearly marked as such, for example by including [preprint] before the reference, and specifically referred to as a preprint in the main text. Where a preprint has subsequently become available as a peer-reviewed article, the formal publication should be used as the reference.

Figures

Our in-house illustrators redraw most figures into *Lancet* style. The quality of the files we receive from authors has a direct effect on the accuracy and time taken to prepare figures that are suitable for publication.

We have different criteria for photographic and illustrative files, the following notes are a summary of our ideal requirements, but a detailed description is in the [artwork guidelines](#)

- For images (photographs or photographic images) that are used as part of illustration or image composite figures we require a file that is no less than 300 dpi when set at its final printed size. Ideal file formats are TIF or JPG
- For trial profiles, study profiles, and CONSORT diagrams, please supply as an editable flow diagram in Word (.doc) or PowerPoint (.ppt) file
- For illustrations (all non-photographic line-work and general drawing) we require editable vector files that contain selectable geometry and fonts (editable text). The editability of files

Formatting guidelines for text, tables, and figures

Guidelines on formatting of text, tables, and figures can be found at <https://www.thelancet.com/pb/assets/raw/Lancet/authors/artwork-guidelines.pdf>

depends on the package they were created in, but as a rule we would prefer to receive any of the following: Adobe Illustrator (.ai) file; Adobe Illustrator or generic .eps files exported from a graphics program; vector-based PDF, PowerPoint, or Word file; or SVG file. If authors are unable to supply files in any these formats, our in-house illustrators can offer guidance on whether it is more economical to export or convert the file into another format, or to redraw from scratch. When files are exported to eps files, we would prefer text to be exported "as text" rather than "as objects", which is especially crucial for files such as forest plots in which there is a lot of text

- If your figures are annotated, please supply two copies of each of these figures as separate files (one annotated copy and one non-annotated and editable copy). Our in-house illustrators will annotate according to journal style using the annotated figures as a guide. For multi-part figures, please supply the individual parts as well as a combined version to be used as a guide for our illustrators to recreate the files
- Images that have been published previously should be accompanied by a statement indicating permission to reproduce the image. If required, further assistance can be obtained from the editorial team. If you have used previously published images, you must obtain permission from the copyright holder of the paper, which might be the authors or the publisher. If all the figures are your own and have not been published before, then this requirement does not apply

Guidelines for supplementary material

All material should be submitted as one PDF (with a table of contents and numbered pages) with the paper and will be peer reviewed. Material will be published at the discretion of *The Lancet* journals' editors. For clinical trials, we encourage authors to include a copy of the study protocol. All material should be provided in English.

Text

- Main heading for the web extra material should be in 12 point Times New Roman font **BOLD**
- Text should be in 10 point Times New Roman font, single spaced
- Headings should be in 10 point **BOLD**

Tables

- Main table heading should be in 10 point Times New Roman font **BOLD**
- Legends should be in 10 point, single spaced
- Tables should be in 8 point Times New Roman font, single spaced
- Headings within tables should be in 8 point **BOLD**

Data

- Numbers in text and tables should always be provided if % is shown
- Means should be accompanied by SDs, and medians by IQR
- p values should be given to two significant figures, unless $p < 0.0001$

Drug names

- Recommended international non-proprietary name (rINN) is required
- We encourage use of neuroscience-based nomenclature for psychotropic drugs

Drug names

For more on neuroscience-based nomenclature see [http://www.thelancet.com/pdfs/journals/lanpsy/PIIS2215-0366\(17\)30098-6.pdf](http://www.thelancet.com/pdfs/journals/lanpsy/PIIS2215-0366(17)30098-6.pdf)

References

- Vancouver style—eg,
Smith A, Jones B, Clements S. Clinical transplantation of tissue-engineered airway. *Lancet* 2008; **372**: 1201–09.

Hourigan P. Ankle injuries. In: Chan D, ed. Sports medicine. London: Elsevier, 2008: 230–47.
- Numbered in order of mention in appendix and numbered separately from references in the full paper

Figures

- All images must have a minimum resolution of 300 dpi, width 107 mm
- Main figure heading should be in 10 point Times New Roman font **BOLD**
- Legends should be in 10 point, single spaced

Audio/video material

- The paper to which the audio or video clip relates should be mentioned in the recording
- Audio clip and video files should be accompanied with brief text explaining the content of the audio, names of interviewers/interviewees, date of recording, and place of recording if relevant
- Written consent from all parties must be obtained (see also the above section on **Patient and other consents**)

Audio

- Audio material submitted as an mp3 file, no larger than 50 Mb
- Your paper may be selected for a podcast. If so, the Web Editor will contact you to arrange a pre-recorded interview to discuss your paper. For more information, see [Audio](#)

Audio
<http://www.thelancet.com/audio>

Video

- Video material should be submitted in .mp4 format with aspect ratio of 16:9, and be no larger than 50 Mb
- We welcome your videos and invite you to submit any video material (reports, interviews, scans, imaging) for consideration in the online journal. Please ensure that all those featured in the video have given permission for publication (see also the previous section on **Patient and other consents**)
- All video files can be submitted alongside your article in EM

Disclosure of results before publication

- Presentation of data at a scientific meeting, as a poster, abstract, orally, on a CD, or as an abstract on the web, or on a preprint server does not conflict with submission to the *Lancet* journals. As a member journal of the International Committee for Medical Journal Editors, *The Lancet Global Health* does not regard results

that are posted in the same clinical trials registry in which primary registration resides as a previous publication, if the results are presented in the form of a brief structured abstract or table

- The *Lancet* journals operate an embargo system, whereby journalists are given access to papers and press releases ahead of publication, allowing them a protected window to develop their stories. We believe that this window can help encourage balanced and accurate coverage of peer-reviewed scientific and medical research to inform public debate. As such, we ask that authors and their institutions refrain from actively seeking media attention for articles that have been submitted to *The Lancet Global Health* or that are available as a preprint. The important steps of thorough peer review and experienced editorial scrutiny and guidance, together with putting research findings into a wider context and highlighting implications for clinical practice, will make the final published paper in *The Lancet Global Health* very different to the submitted or preprint version. Coverage that results from pre-publication communication can impact media interest at the time of publication and our ability to support responsible journalism
- For more information on Preprints with *The Lancet*, please see www.thelancet.com/preprints. For additional questions regarding media, please contact pressrelease@lancet.com

Online publication

- *The Lancet Global Health* publishes papers online as they become ready. You will be informed at least a week in advance of the Online publication date

How *The Lancet Global Health* handles your paper

Acknowledgment

- Receipt of your paper will be acknowledged by an email containing a reference number, which should be used in all future communications

Checking for plagiarism, duplicate publication, and text recycling

- At our discretion, material that we are interested in publishing will be checked by editors using CrossCheck (see *Lancet* 2011; 377: 281–82). We expect that such papers are written in a way that offers new thinking without recycling previously published text.

Peer review

- *The Lancet Global Health* operates a single-anonymised peer-review process
- Every Article and Meta-analysis published in *The Lancet Global Health* has been peer reviewed. Occasional contributions (eg, Commentaries) are accepted without peer review
- On submission to *The Lancet Global Health*, your report will first be read by one or more of the journal's staff of physicians and scientists. This is an important feature of our selection process and many papers are turned away on the basis of in-house assessment alone. That decision will be communicated quickly
- Research papers are followed by peer review by at least three reviewers. You will receive notification of which editor is handling the peer review of your paper.

Decision

- Submissions that survive in-house and peer review might be referred back to authors for revision. This is an invitation to present the best possible paper for further scrutiny by the journal; it is not an acceptance
- Authors should give priority to such revisions; the journal will reciprocate by making a final decision quickly
- Two copies of the revised version should be sent back, one of which should be highlighted to show where changes have been made. Detailed responses to reviewers' comments, in a covering letter, are also necessary

The *Lancet* journals and other Elsevier journals

- If your paper is rejected by *The Lancet Global Health*, we might judge it suitable to pass to other editors in the *Lancet*-group for consideration or to editors of other relevant journals within Elsevier's portfolio

Appeals

- Sometimes editors make mistakes. When we do, we like to hear about them. If an author believes that an editor has made an error in declining a paper, we welcome an appeal. In your appeal letter, which should be sent to globalhealth@lancet.com, please state why you think the decision is mistaken, and set out your specific responses to any peer reviewers' comments if those seem to have been the main cause of rejection
- At least two editors will decide whether to invite a revised manuscript and whether re-review, or otherwise, is indicated

Proofs

- *The Lancet* journals employ highly skilled Assistant Editors, and it is likely that your paper will be substantially edited after acceptance to ensure that it is accurate, clear, and understandable to a wide readership
- All figures will be redrawn into *The Lancet Global Health* style by our in-house illustrators
- You will receive a proof from an Assistant Editor. That proof should be corrected and returned within 48 h

Editorial research

- We are keen to better understand and improve editorial conduct, decision making, and issues related to peer review. Therefore, we occasionally take part in or conduct editorial research. Your submitted paper might be used in such research. If you do not want your paper entered into such a study, please let us know in your covering letter. Your decision to take part or not will have no effect on the editorial decision on your paper

Open access policy

- *The Lancet Global Health* is fully open access (gold OA), which means that all the content is immediately and freely available to anyone.
- To support the costs of publishing including reviewing (first by internal review, and then [external peer review](#)), technical, copy editing, typesetting and graphics, online hosting, archiving, and promotion, authors who choose to publish OA in our journals

pay an article processing charge (APC), upon acceptance. The APC is payable for all full-length peer-reviewed article types. Information on the APC for *The Lancet Global Health* can be found at <https://www.thelancet.com/open-access>.

- The decision to accept or reject a paper at *The Lancet* Group is conducted by peer-review Editors and is not related to the ability to pay. Editors do not have access to payment information upon submission, and payments post-acceptance are handled by a separate department.
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Ombudsperson

For information about what our ombudsperson can and cannot

investigate, articles about past ombudspeople, and how to contact the current ombudsperson see <https://www.thelancet.com/ombudsperson>.

What happens after publication?

Press release

Press releases are issued by *The Lancet* journals' press office for selected content published in our journals. You will be advised in advance if your paper has been selected for press release. *The Lancet* journals' media relations team will contact you with detailed instructions about the embargo for your paper, and will provide a draft press release for your comments ahead of the publication date. If your institute or funder are planning to press release your paper, please let your Assistant Editor know in the first instance, and they will provide you with details on *The Lancet's* press release policy, embargo dates, and how to receive finalised PDFs of your paper to share with journalists.

Author interview

Your paper may be selected for a podcast. If so, the Web Editor will contact you to arrange a pre recorded interview to discuss your paper. For more information, see [Audio](#)

Data storage

Authors may be required to provide the raw data for research papers when they are under review and up to 10 years after publication in *The Lancet Global Health*

Responsible sharing

The Lancet supports responsible sharing. We recognise that authors want to share their papers and we encourage this. Find out how you can share your paper [here](#).

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