



CHAMPS

**Building
Knowledge.
Saving
Children's
Lives.**

December
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Child Health and Mortality Prevention Surveillance Network Manual

Version 1.0



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Acronyms & Abbreviations

AFB	Acid-Fast Bacteria
AMR	antimicrobial resistance
CBR	Central Biorepository
CDC	Centers for Disease Control and Prevention
CDCC	CHAMPS Data Change Committee [<i>proposed</i>]
CHAMPS	Child Health and Mortality Prevention Surveillance Network
CHAMPS DS	CHAMPS Diagnosis Standards
CHAMPS ID	CHAMPS Identification
CHAMPS IT	CHAMPS Information Technology
CHAMPS PO	CHAMPS Program Office
CPL	Central Pathology Laboratory (Infectious Diseases Pathology Laboratory, CDC)
CRF	Case Requisition Form / Case Report Form
CMV	Cytomegalovirus
CSF	cerebrospinal fluid
Ct	cutoff
DBS	dried blood spot
DeCoDe	determination of the cause of death
DS	Diagnosis Standards
DNA	deoxyribonucleic acid
DDCM	Data and Diagnostic Change Management (Process)
DSS	Demographic surveillance systems
EDTA	ethylenediaminetetraacetic acid
FFPE	formalin-fixed, paraffin-embedded
GA	gestational age
GD	guidance document
GMS	Grocott methenamine silver
GN	Gram negative
H&E	Hematoxylin and Eosin
HDSS	health and demographic surveillance systems
HIV	Human Immunodeficiency Virus
HSV	Herpes simplex virus
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
ICD-PM	Application of ICD-10 to Deaths During the Perinatal Period (Perinatal Mortality)
ID	identifiers/identifications
IHC	immunohistochemistry
ISGlobal	Barcelona Institute for Global Health
IUFD	intrauterine fetal distress
LabKey	software used to integrate, analyze, and share CHAMPS data
MITS	minimally invasive tissue sampling
MUAC	mid-upper arm circumference
N/A	Non-Applicable
NA	nucleic acid
NEG	Negative
NGS	next-generation sequencing
NP	nasopharyngeal
PAS	Periodic Acid Schiff
PCR	polymerase chain reaction
Pf	<i>Plasmodium falciparum</i>
POS	Positive
PPE	personal protective equipment
QA	quality assurance

QC	quality control
QS7	Quant Studio 7 Flex
REDCap	software for developing and submitting CHAMPS forms
RDT	rapid diagnostic test
RNA	ribonucleic acid
<i>rpoB</i>	gene encoding rifampin resistance
RSV	respiratory syncytial virus
RT-PCR	Reverse-transcription polymerase chain reaction
RT-qPCR	Quantitative reverse transcription PCR
SBS	social-behavioral sciences
SOPs	standard operating procedures
SQL	a domain-specific language used in programming
SS	special stains
SURPI	Sequence-based Ultra-Rapid Pathogen Identification
TAC	TaqMan Array Card
TB	<i>Mycobacterium tuberculosis</i>
TBD	to be determined
TORCHZ	<i>Toxoplasma</i> , rubella, cytomegalovirus, herpesviruses, <i>Treponema</i> , and Zika;
U5	under 5 (years of age)
UG	user guidance
VA	verbal autopsy
ViiA 7	ViiA 7 Real-Time PCR System
W-S	Warthin-Starry
WHO	World Health Organization
ZNAFB	Ziehl-Neelsen acid-fast bacilli

Executive Summary

The Child Health and Mortality Prevention Surveillance (CHAMPS) Program aims to identify and collect data on causes of stillbirths and deaths of children under 5 years of age, in areas of sub-Saharan Africa and South Asia with high infant and child mortality. The CHAMPS Program is designed to apply advanced laboratory methodologies, diagnosis standards and a systematic approach to obtain more reliable and accurate data for causes of child deaths and stillbirths to inform public health actions.

The purpose of this manual is to describe the standardized procedures and processes for determining cause of death across the CHAMPS Network and to serve as a reference for training and quality management. The manual includes an overview of the CHAMPS Mortality Surveillance process, from death notification through determination of cause of death and family follow-up. Key features of the CHAMPS approach are highlighted, including the use of minimally invasive tissue sampling (MITS), systematic approach to determination of cause of death (DeCoDe), and approaches to quality management and standardization of processes and data collection.

The manual is based on the initial CHAMPS Laboratory and Diagnostics Plan and the objective of the manual is to provide in one document information and access to all the current procedures and processes used for determining cause of death across the CHAMPS Network, including all current Standard Operating Procedures (SOPs), associated forms, guidance documents and other related materials and references.

The manual will continue to be updated to reflect current processes and procedures utilized at CHAMPS Network sites, including best practices and lessons learned, to improve the efficiency of processes and the accuracy of CHAMPS data and results.

I. Overview of CHAMPS

1. Introduction to CHAMPS

A. The CHAMPS Program

The overall goal of the Child Health and Mortality Prevention Surveillance (CHAMPS) Program is to obtain more reliable and accurate data about causes of stillbirths and deaths of children under 5 years of age (U5), in order to more effectively target interventions and reduce mortality rates. The program is focused in areas of high infant and childhood mortality in Sub-Saharan Africa and South Asia. Briefly, the main overall objectives are to:

- track definitive causes of child mortality in sites in Sub-Sahara Africa and South Asia;
- produce and disseminate high-quality data to inform policy and health actions; and
- build in country capabilities and enable CHAMPS Network sites to leverage CHAMPS investment to prevent U5 child mortality.

Seven sites were selected initially to participate in the CHAMPS Network in the following countries: Bangladesh, Ethiopia, Kenya, Mali, Mozambique, Sierra Leone and South Africa.

CHAMPS data, and Determination of Cause of Death (DeCoDe) results specifically, will help prioritize limited resources and inform actions to save lives and reduce child deaths from preventable diseases in network countries. Additionally, incorporation of DeCoDe results into the [Global Burden of Disease](#) and similar global estimation efforts should improve overall accuracy of global mortality statistics.

Recent publications provide detailed descriptions of the CHAMPS Program, the need for better cause of death data, and the criteria for selecting the sites and the approaches that were developed to achieve CHAMPS goals [1- 3; [The Child Health and Mortality Prevention Surveillance \(CHAMPS\) Network: Foundational Methods](#)]

B. The CHAMPS Approach to Mortality Surveillance

The CHAMPS approach includes community engagement, demographic surveillance, mortality surveillance, case enrollment, cause of death determination and data to action activities.

Before the initiation of CHAMPS activities at each site, considerable preliminary community engagement activities take place to assess acceptability of CHAMPS and the minimally invasive tissue sampling (MITS) procedure. At each site a social and behavioral sciences (SBS) team is established to examine local social, cultural, and religious customs, explain the project aims and methods, and seek community support. The information gathered by SBS teams informs culturally appropriate interactions with family members for enrollment and consenting, interviewing family members and communicating results to parents. Site SBS teams conduct focus groups, assist with rumor identification and mitigation, support families, and engage the community to ensure the feasibility and sustainability of CHAMPS activities [4,5].

Demographic surveillance systems (DSSs) are used to monitor populations and their health over time within a geographically defined surveillance area. The CHAMPS DSSs provide demographic data for estimating population-based mortality rates and health information associated with the deaths of children U5. The longitudinal data collected for CHAMPS includes core data elements required for calculating mortality rates (age and sex-specific population size and numbers of deaths; sex-specific number of births; in and out migrations), and additional data on household environmental factors and indicators of maternal and child health and nutrition status. The CHAMPS program requires each site's DSS (or if it includes health data, Health and

Demographic Surveillance System (HDSS)) to conduct at least twice-yearly rounds of collecting data on births, deaths and population characteristics, but some network sites conduct additional rounds to better track pregnancies and migrations [6].

CHAMPS sites have established mortality notification systems to report potentially eligible stillbirths and U5 deaths within the defined CHAMPS catchment areas [3] as described in the CHAMPS Mortality Surveillance Process section. CHAMPS actively monitors death notifications with the aim of improving timeliness of death notifications from facilities and communities, and to ensure that all causes of death for children U5 including stillbirths are represented [3].

All sites have received approval from the appropriate ethics review committees to conduct CHAMPS mortality surveillance. The CHAMPS Program Office (PO), based at Emory University, has received approval from the Emory University Institutional Review Board.

Some of the key features of the approach to the CHAMPS mortality surveillance and DeCoDe, are described below:

Minimally Invasive Tissue Sampling Procedure

Central to the CHAMPS approach for DeCoDe, is the use of the MITS procedure instead of conducting a full autopsy to obtain specimens from deceased children U5. The procedure consists of sampling fluids and key organs using biopsy needles followed by microbiological and histopathological analysis.

The MITS procedure has been shown to be a good alternative to conducting a full autopsy in low resource settings, especially for death due to infections and malignant tumors, and to be more acceptable to the families of deceased children [7]. Pilot studies in South Africa for example, showed an encouraging rate of consenting by parents of deceased children and an interest by the parents in obtaining the results regarding their deceased infant or child [8].

Cause of Death Determination Process

The evaluation of each death includes a review of the clinical story from the verbal autopsy (VA), supplemented by the hospital records of children and mothers, postmortem laboratory results and pathology reports of specimens obtained by the MITS procedure (see **Figure 1**).

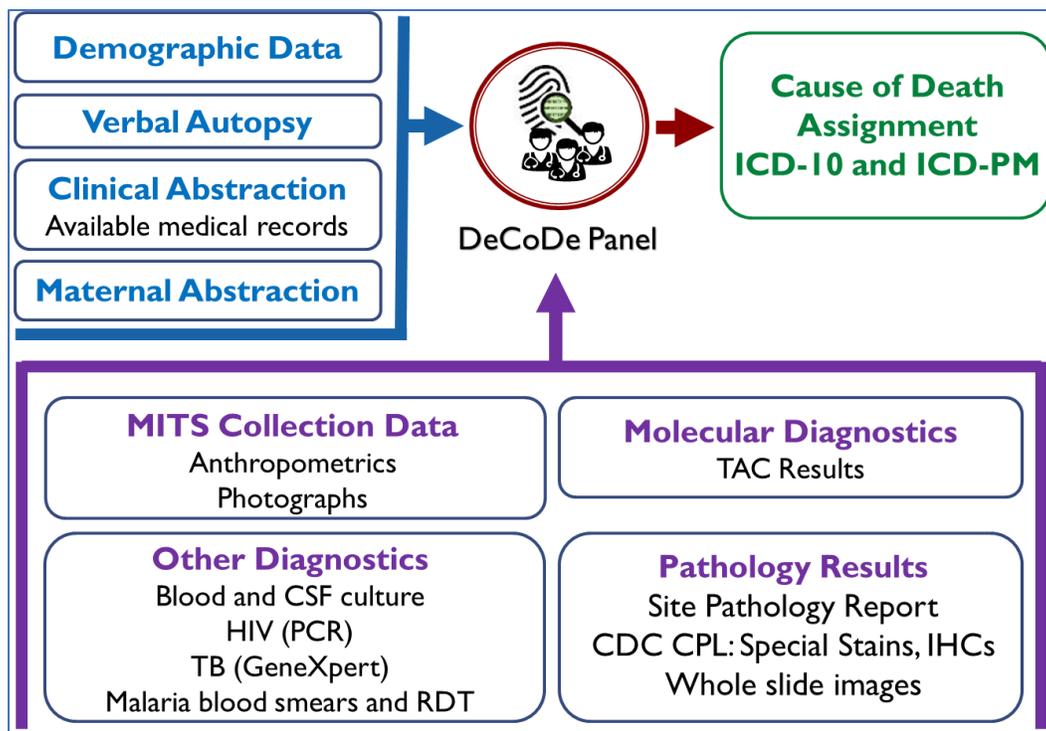


Figure 1: High-level overview of the DeCoDe process outlining components that contribute to cause of death determination.

A consensus process for DeCoDe for stillbirths and U5 child death across the CHAMPS Network has been developed using multidisciplinary panels of experts from each site. The site panel uses the information provided to assign a cause of death in accordance with the International Classification of Diseases, Tenth Revision (ICD-10) and the World Health Organization (WHO) Medical Certificate of Cause of Death. The CHAMPS Diagnosis Standards (CHAMPS DS) have been developed (see DeCoDe [Standard Operating Procedures and Forms](#) and [Supplemental Materials](#)) to support cause of death determination and a more consistent interpretation of data across the CHAMPS Network. Standardization of DeCoDe for CHAMPS will enable future comparability with other sources of mortality data produced by initiatives external to CHAMPS. The detailed information used for DeCoDe will allow for the more definitive assignment of the full causal chain and cause of death for children in areas of highest mortality rates [9].

A summary of CHAMPS information about MITS cases conducted to date and current cause of death data can be accessed via the following links: [Enrolled Population Summary](#), [Cause of Death Data](#), and [CHAMPS Dataverse](#).

Standardization of Processes and Procedures

Standardization across CHAMPS Network sites is a critical feature of the CHAMPS approach. The CHAMPS Network sites are spread across multiple geographic locations, with differences in infrastructure and staff, and it is therefore essential to standardize all the procedures across the network, in order to reduce site specific variations. Moreover, the volume and complexity of data collected and the need for coordination between different data collection processes within and between sites, also requires standardization of data collection instruments, establishing data quality specifications and implementing robust data quality monitoring solutions (for additional information see section on [Data Quality](#)).

Ensuring the quality of all laboratory and clinical data is essential for achieving a key CHAMPS objective to provide accurate, timely and reliable data on causes of deaths of stillbirths and children U5.

2. CHAMPS Mortality Surveillance Process

A. Overview

A high-level workflow summary of the process starting with death notification through contacting family with cause of death determination results presented in **Figure 2** below.

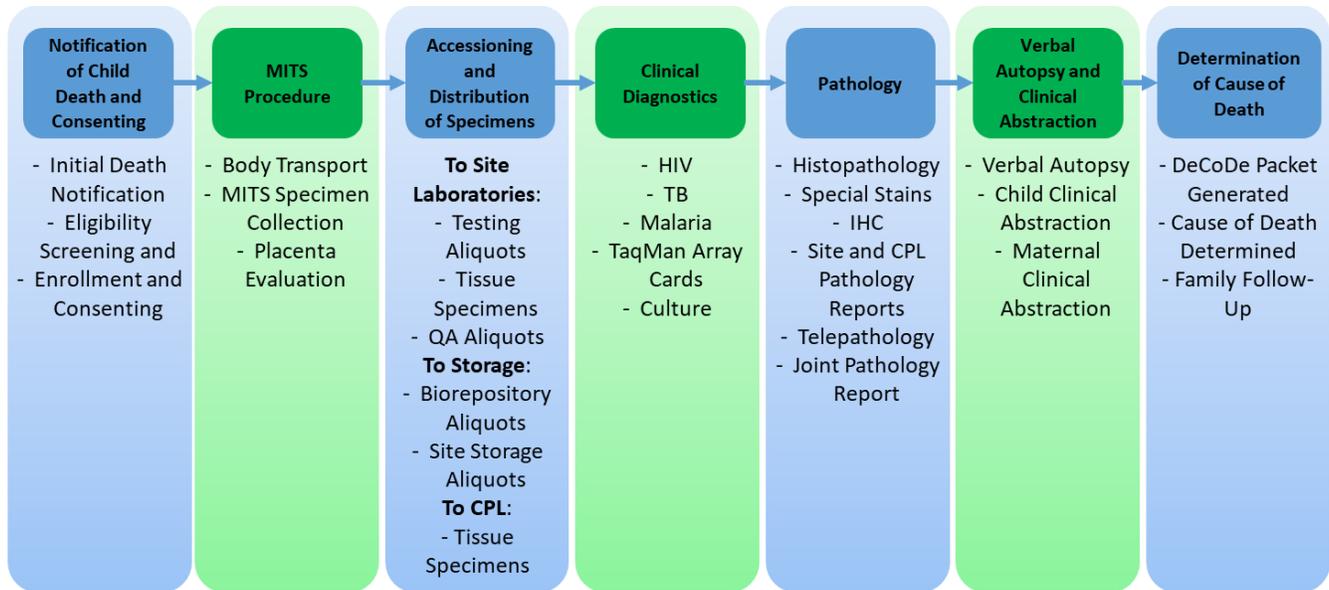


Figure 2: Overview of the CHAMPS diagnostic process starting from consent to family notification.

Initial Death Notification: The process is initiated with notification of the death of a child in a CHAMPS catchment area, that took place either in a facility or in the community. Eligibility criteria for enrollment includes residence of mother and child in the catchment area; age of deceased child <60 months or stillbirths; and time of death after initiation of CHAMPS mortality surveillance at the site. In order to be eligible for MITS, death must be reported within 24-36 hours (can be extended if the body is refrigerated shortly after death). For additional information see Death Notification and Eligibility Screening SOP (06.01.01).

Eligibility Screening and Consenting: A consenting team, comprised of a health worker and staff trained to provide counselling as needed, approaches the family or guardian to confirm eligibility and obtain consent for collecting data and performing the MITS procedure. Consent procedures have been adapted to each CHAMPS site, based on local SBS team recommendations [3]. The consent for MITS procedure allows for collecting specimens and photographs, performing laboratory tests, shipping and storing specimens, extracting clinical data and contacting the parents with results. The family member or guardian may opt out of the MITS procedure and agree only to VA and clinical records abstraction, as shown in **Figure 3** below, referred to as the Non-MITS process. For additional information see Death Notification and Eligibility Screening SOP (06.01.01).

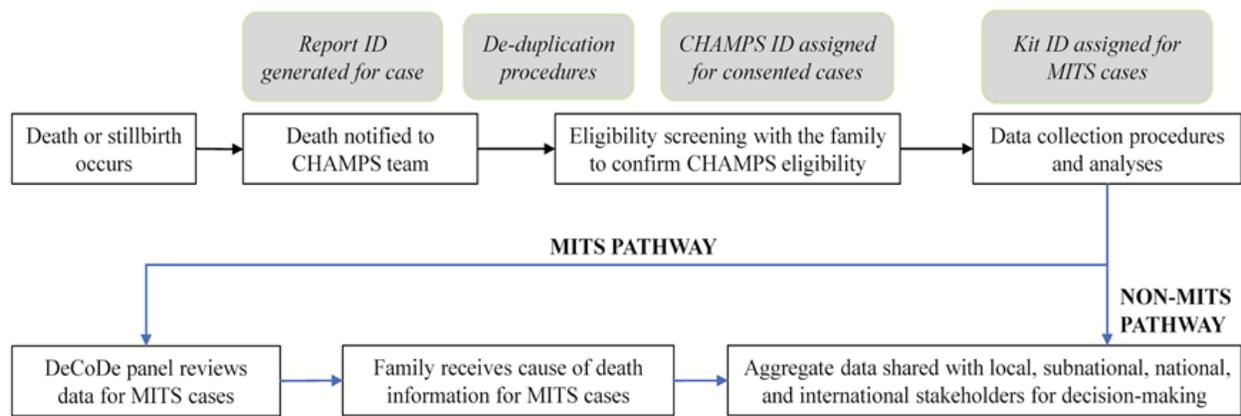


Figure 3: Overview of CHAMPS Mortality Surveillance procedures [3].

Consent Tracking and Authorization: The Informed Consent Forms adapted for each site, provide several options for families to participate in the full MITS procedure, data collection and re-contacting after MITS, or to consent only to data collection (Non-MITS), or withdraw consent to participate. CHAMPS tracks information about consent and withdrawal from the study, using specific forms to ensure that all activities are conducted with the appropriate consent. For additional information see Consent Process SOP (06.01.02).

MITS Procedure: For cases consented for the MITS procedure, the body is transported to the location where the MITS procedure is performed, and the body is released to the family after MITS and transported for burial, as appropriate for each site. For deaths detected in the community depending on the site, consent is obtained to transport the body to a pre-determined private location either in a health facility, specially equipped vehicle, or mobile site, based on discussions with site leadership and site-specific ethnographic information. For deaths identified in a health facility, after consent is obtained, the body is moved to a private room at the facility for the MITS procedure [3].

The MITS procedure includes preparation of the body, gross examination, measurements and photography, specimen collection, and recording information as described in the SOP (see [Minimally Invasive Tissue Sampling](#)). The placenta is also evaluated as described in detail in the MITS Procedure SOP.

Accessioning and Distribution: Specimens collected during the MITS procedure are transported to a laboratory, accessioned and distributed or shipped for testing (see [Specimen Accessioning and Distribution](#)). A set of specimens are frozen for future use and stored at a biorepository either at the CHAMPS Network site or shipped to a central long-term storage location. In addition, a subset of specimen aliquots is reserved for quality assurance (QA).

Clinical Diagnostics: Microbiology culture and molecular tests are performed on selected specimens. Testing includes specific assays for human immunodeficiency virus (HIV), *Mycobacterium tuberculosis* (TB), malaria and an array of infectious agents via TaqMan array cards (TAC) (see [Clinical Diagnostics](#) and [TaqMan Array Cards \(TAC\)](#)).

Pathology: Histopathology is performed on formalin-fixed paraffin embedded tissue specimen at the sites and at the Centers for Disease Control and Prevention (CDC) Central Pathology laboratory (CPL); special stains (SS) and immunohistochemistry (IHC) are carried out as needed. Sites and the CPL discuss findings during telepathology sessions. The sessions allow both the sites and CPL to review digitized and annotated site and CPL-generated

slides for concordance as well as QA, training and research purposes (see [Clinical Diagnostics](#) and [CPL and Telepathology](#)).

Verbal Autopsy and Clinical Data Abstraction: For all enrolled cases, consent is requested to conduct a VA interview with a parent, other family member, or caregiver close to the child. The VA is conducted according to WHO VA guidelines. VA data are analyzed by automatic diagnostic algorithms, such as OpenVA (OpenVA is software for Verbal Autopsy) [3] (for more information see section on **Verbal Autopsy**).

Available clinical information for the deceased child and relevant maternal health information is abstracted for enrolled MITS and non-MITS cases. The completeness of data varies by site. Clinical records may be obtained from all types of health facilities involved in the child's and mother's care, including antenatal care clinical or obtained from family members [3] (for more information see [Clinical Abstraction](#)

Determination of Cause of Death (DeCoDe): A panel of experts is assembled at each site and provided with a case packet containing information (see [Determination of Cause of Death](#)). The site panel uses the information to ascertain the underlying cause (event that precipitated the fatal sequence of events) and other antecedent/comorbid and immediate, causes of death in accordance with the ICD-10 guidelines. Additionally any maternal factors in perinatal deaths are collected in accordance with ICD-PM. CHAMPS DS have been developed (see [Supplemental Materials](#)) providing a framework of required evidence to support cause of death determination. Every DeCoDe panel has a member trained to complete the death certification in accordance with the WHO Medical Certificate of Cause of Death [9].

Family Follow-Up: The child's parents (or guardian and other close relative, as appropriate) are provided results of testing, cause of death determination, and referred to applicable services and resources as needed (see [Family Follow-up](#)) [3].

B. Quality Management

The CHAMPS procedures are designed to incorporate quality management approaches described below. Where applicable, certain sections of the manual contain QA and quality control (QC) measures pertaining to the procedures described in that section.

Standardization: As mentioned above, given the geographic distribution of the network sites and differences in infrastructure and staffing, the SOPs and forms described throughout and attached in the appendix, have been developed to facilitate standardization of procedures and processes across the entire CHAMPS Network (see [Master List of Standard Operating Procedures, Forms, and Other Documentation](#)). The SOPs, forms and other documents contain quality-related questions and notes to guide site personnel as they perform the various procedures. Some SOP associated forms include instructions and explanations to ensure accurate and complete data entry (see [Forms](#)).

Training: Training is provided for the steps involved in mortality surveillance and DeCoDe processes described above, such as notification of cases, enrollment and consenting adapted to sites based on SBS results and includes training for counseling and interacting with family members of deceased children [3].

The CHAMPS PO also developed training modules for data collection that are adapted according to site specific procedures and requirements and include, for example, procedures for death identification, assignment of CHAMPS IDs, linkage and de-duplication of data, death notification, general biosafety, VA and clinical records

abstraction procedures. Experts in the CHAMPS PO and partners such as CDC and Barcelona Institute for Global Health (ISGlobal) provide training and assistance to sites.

Training is provided anytime a new site is launched and the first MITS procedures are performed and testing is initiated. Specific on-site training is provided also for MITS and TAC procedures [10, 11, 12]. Review of digitized histology slides during telepathology sessions also provide opportunities for both training and QA [11]. Training and guidance are provided also when the DeCoDe Panel is assembled for the first time to review cases [9].

Biosafety and Infection Prevention and Control: Biosafety and infection prevention and control guidance is provided to ensure safe working conditions for the personnel and the surrounding environment. Practicing appropriate biosafety and infection prevention and control procedures are critical for transporting the body, performing the MITS procedure, transporting and shipping the specimens, storing the specimens, and testing specimens. SOPs, guidance documents, and supplemental materials such as the Biosafety Guidance for MITS Procedure (GD 06.02.07), Guidelines for Infection Prevention and Control (UG 06.01.04), and Biosafety in Microbiological and Biomedical Laboratories 5th Edition, provide best practices, visual aids, recommendations, and references for personnel safety and prevention of cross-contamination, maintaining appropriate testing environments and laboratory equipment, and handling specimens.

C. Data Quality

The descriptions below are focused on factors impacting cause of death determination, from death notification through communicating results to the family.

Mortality surveillance and death notification procedures are developed by surveillance teams at each site and are informed by SBS research. Sites use various approaches such as call centers, cell phones and text messaging via community reporters to receive death notifications. The goal is to implement both facility- and community-based notification systems.

The CHAMPS ID system provides unique IDs for tracking initial cases, consented and enrolled cases, mothers consenting to maternal abstraction and linking the pregnancy event to the deceased child. In addition, the CHAMPS ID system provides a unique MITS specimen collection kit ID to each MITS performed. Each kit contains pre-labeled collection containers with barcoded specimen ID labels along with labels for extra specimens. The specimen ID number is a combination of the specimen kit ID and a component ID that identifies the type of specimen collected. The linkage of CHAMPS ID to specimen kit ID enables the linking of any laboratory result to a specific MITS death.

Enrollment procedures are standardized per site and capture consent and level of consent (non-MITS versus MITS). Following consent, the data collection process proceeds with MITS specimen collection, children and maternal clinical data abstraction, and VA. The cause of death determination process starts once all data is collected, testing is completed, and the information is compiled in a DeCoDe Case Packet for DeCoDe panel members to review. A unique version identifier and date/time stamp is created each time a DeCoDe Case Packet is created, enabling regeneration of the packet if new information is added, or if a new panel reviews and provides another set of cause of death results.

CHAMPS Data Quality Monitoring System

CHAMPS aims to improve cause of death determination through the collection of comprehensive VA, clinical, laboratory and histopathological data. The DeCoDe Panel at each site reviews all available data to determine cause of death. Optimally, the objective is to determine the cause of death within 120 days of death. The timeline requires an agile data quality process that can ensure accuracy, completeness and consistency prior to the DeCoDe Panel. The CHAMPS Data Quality Monitoring System utilizes REDCap for data collection and real-time data quality rule execution, SQL Server for relational data storage and complex data quality algorithms that run daily on a reporting database, and LabKey for end-users to access the most recent data quality reports.

REDCap (Research Electronic Data Capture), is a browser-based, metadata-driven electronic data capture software and workflow methodology for designing clinical and translational research databases [13]. The forms mentioned throughout this document can be found electronically via REDCap. The forms hyperlinked in the appendix or located in the SOP appendices are for instructional and informational purposes only. REDCap or approved laboratory information management systems should be used for all data entry for CHAMPS cases. LabKey Server is an open-source software platform designed to help research organizations integrate, analyze, and share complex biomedical data [14].

The volume and complexity of the data collected, requires dynamic and comprehensive data quality monitoring solutions. The following details elements particular to each tool utilized in the data quality system. These systems interact to form a robust data quality system across multiple platforms (see **Figure 4**).

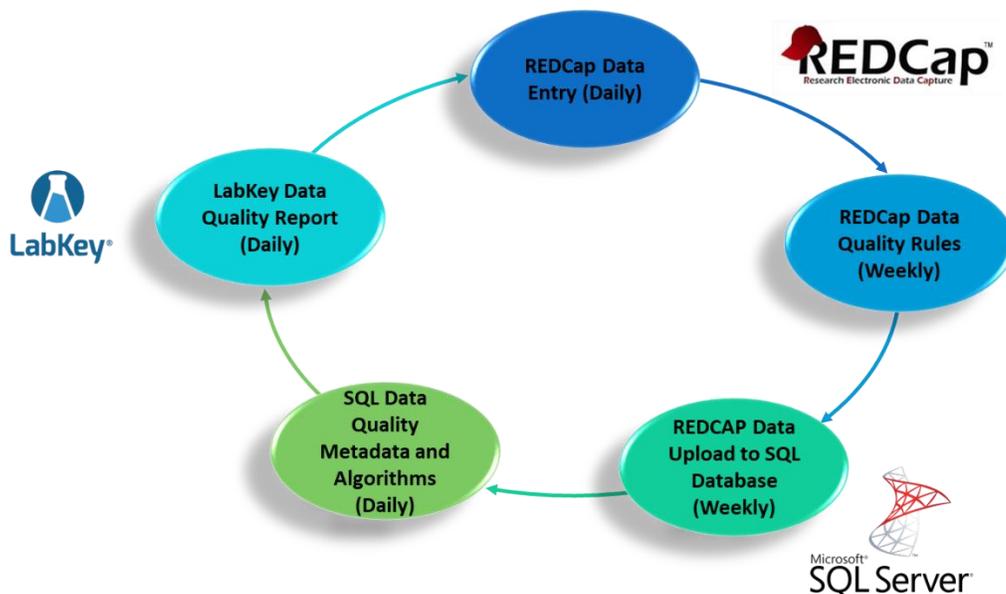


Figure 4: CHAMPS Data Quality Cycles

Data Quality MetaData:

- Unique QualityID (e.g., Q00011)
- Error notification name (e.g., *Died before Born*)
- Error notification resolution (e.g., *Date of birth should be on or before date of death*)

- REDCap data quality rule syntax
- Data Quality code version number (e.g. *Version 3.0.0*)

SQL Algorithm:

- One row per unique record and QualityID flagged
- SQL database contains all data types from all sites
- Dynamically queries all data for standard issues
- Table truncates/inserts results from view for stability

REDCap Data Quality Rules:

- REDCap syntax is different than SQL syntax
- Same logic as SQL algorithm, so same data quality issues
- Implementation required complex coding to enable the REDCap data quality rule syntax to be embedded in the SQL metadata reference table without triggering execution.

LabKey and Communication

- Daily LabKey refresh – shows data quality issues for sites
- Weekly emails – site data manager to resolve issues
- Monthly Calls – high-level process improvement issues

This dynamic system facilitates collaboration and adherence to cross-network standards, generating high-quality data for the case-level cause of death review (DeCoDe panel) as well as reliable aggregate data for analysis and visualization.

Data quality codes (as illustrated in **Table 1**) have been developed to address 5 significant data quality challenges:

Illogical or Impossible Scenarios: Flags scenarios that should not occur (e.g., a case’s documented date of death is before the date of birth). Cross-project data quality rules are helpful for identifying these scenarios.

Timeliness: Flags specific elements for a case that have not been received by the CHAMPS PO within an expected timeframe (e.g., missing laboratory data for a case that consented to specimen collection many weeks ago). Because the goal is to determine cause of death within 120 days, timeliness is critical.

Out of Range (Abnormal Numbers): Flags numeric result values that require validation (e.g., 700 kg child or 40,000% RBCs infected with malaria).

ID Formatting: Flags improperly formatted IDs (e.g., champs IDs, kit IDs, and specimen IDs). IDs are essential in linking data together for the DeCoDe panel reports.

Missing Data: Flags essential elements that have not been transmitted to the CHAMPS PO (e.g., missing dates, demographic fields).

Quality ID	Resolution	Problem Addressed
Q00012: Notified Before Died	Date of death should be on or before date of death notification	Illogical or impossible scenario

Q00033: MITS no Kits	Verify MITS consent; if consent was granted, there must be a specimen kit ID assigned or reason given for MITS not being performed	Timeliness
Q00041: Weight Check	Verify that weight entered is between 0 and 30 kilograms	Out of range
Q00060: TB DNA Lung Specimen ID	The specimenID should be MXXXXX.039 or MXXXXX.040	ID formatting
Q00088: Location of Death Missing	Please enter the location of death in the Child Abstraction, VA, Eligibility Screening or Death Notification as appropriate	Missing data

Table 1: Example Data Quality Rules and Resolutions

As the CHAMPS Network matures and expands, the Data Quality Monitoring System will adapt and improve in response to analytic priorities, data collection form improvements, and key inputs into the DeCoDe process.

D. Data and Diagnostic Change Management Process

To facilitate the effectiveness and efficiency of the CHAMPS Program and to meet objectives, the Data and Diagnostic Change Management Process has been developed. The process will allow the CHAMPS Network to submit change requests to CHAMPS PO for evaluation and recommendation. A brief overview of the purpose and process are described below.

The purpose of the Data and Diagnostic Change Management (DDCM) process document is to describe the roles and responsibilities within and outside the CHAMPS PO as they relate to types and classes of change requests, the documentation and assessment change requests, documentation of leadership recommendations and management of approved change request implementation. The DDCM process will objectively, transparently and consistently manage submitted change requests that will impact CHAMPS data collection and diagnostic processes starting from notification and including the MITS procedure through DeCoDe Case Packet generation.

Briefly, a CHAMPS Change Request Form is submitted by a Change Requestor to the Change Manager by September 1st each year. The Change Manager coordinates impact assessments from subject matter experts, Site Strategy and Implementation (S³I), Data Sciences and Access, and Business Operations teams. The change request is presented to the proposed CHAMPS Data Change Committee (CDCC) [*proposed*] who provide recommendations for each change request. The Change Manager documents all CDCC [*proposed*] recommendations, communicates the decisions to the respective Change Requestors and records change request in the Change Registry. The Change Manager oversees implementation of all approved change requests.

3. Scope and Purpose of the CHAMPS Manual

The purpose of this manual is to standardize procedures and processes and serve as a reference for training and quality management for the CHAMPS Network. The manual includes all the current procedures used for determining cause of death across the CHAMPS Network (see [Master List of Standard Operating Procedures, Forms, and Other Documentation](#)). This manual, based on the initial CHAMPS Laboratory and Diagnostics Plan [15], was developed to specify the diagnostic procedures and protocols involved in the CHAMPS mortality surveillance and determination of cause of death activities. This manual does not currently include demographic surveillance and social and behavioral aspects of the CHAMPS Program.

The main objectives as stated in the original Laboratory and Diagnostics Plan [15] are:

- to collect data using standardized procedures across all surveillance sites;
- minimize biases in data collection, processing, and analysis;
- employ QC and external QA along with site-specific quality improvement;
- routinely evaluate and reassess processes and procedures on a regular basis based on evaluation of data; and
- convene technical expert panels to advise on updates to laboratory procedures.

The manual is divided in sections describing the processes and procedures starting from the MITS procedure through family follow-up. Each section includes a brief description of all the relevant SOPs and related forms and guidance documents, highlighting items requiring special attention and any items that have been recently added, changed or updated.

This manual will continue to be updated to reflect current processes and procedures utilized at CHAMPS sites, including best practices and lessons learned to improve the efficiency and accuracy of the DeCoDe process.

II. Laboratory and Diagnostic Procedures

As described in the introductory overview, participating CHAMPS Network sites are spread across multiple geographic locations, with differences in infrastructure and staff. To minimize site-specific variations and ensure reliability of data used for cause of death determinations, it is essential to standardize procedures across the CHAMPS Network. Section II describes the MITS procedures, Specimen Accessioning and Distribution, Clinical Diagnostics, TaqMan Array Cards (TAC), CPL and Telepathology, Pilots and Studies Under Consideration, and Non-Diagnostic Data Collection.

The following subsections highlight SOPs, forms and related materials that were developed to assist CHAMPS Network sites with standardization of laboratory and diagnostic procedures (see [Master List of Standard Operating Procedures, Forms, and Other Documentation](#)). The SOPs and related forms described will continue to be developed and modified in order to improve quality and efficiency of laboratory testing.

1. Minimally Invasive Tissue Sampling

A. Introduction to MITS and Specimen Collection

Once eligibility is evaluated and consent obtained, the body is transported to a designated facility where the MITS procedure is performed. The section below describes the SOPs and related documents developed by the CHAMPS PO to assist sites and ensure that adequate quantity and high-quality samples are obtained for subsequent testing; correct identifiers (IDs) are assigned, data collection forms are complete and accurate and biosafety procedures are implemented for all involved personnel and the environment.

The downstream testing and results that will inform DeCoDe are critically dependent on the correct performance of the MITS procedure. The MITS Procedure SOP includes specific instructions for collection of each specimen type. The associated MITS Specimen Collection Form provides specific instructions for accurately and completely documenting the collection of specimens, observations and any deviations from the MITS procedure SOP.

B. Standard Operating Procedures and Forms

The following provides a brief overview of the SOPs, forms and guidance documents (see [Master List of Standard Operating Procedures, Forms, and Other Documentation](#)) related to the MITS procedure.

Transfer of Body SOP (06.01.03)

The purpose of the Transport of Body SOP is to standardize the procedure for transporting a body intra-facility (within a facility), from another health facility, or from the community to the MITS collection facility and returning the body to a designated entity (i.e., family, morgue, etc.). The SOP also defines roles, responsibilities and necessary materials.

Disposition of Body Form (CRF 06.01.03)

The Disposition of Body Form is used to record the transfer of the body to a designated entity (i.e., family, morgue, etc.) for burial after the MITS procedure is completed.

MITS Procedure SOP (06.02.01)

The MITS Procedure SOP describes in detail the roles, equipment, and steps for collecting tissue and non-tissue specimens (see **Figure 5** below). The SOP describes the order of operations starting from verifying identify, preparing the body, performing anthropometric measurements; inspecting, photographing, cleaning and

sterilizing the body; collecting non-tissue and tissue specimens, ending the procedure and releasing the body back to the family for burial. Following each step in the procedure, there are reminders to record all applicable data into the MITS Specimen Collection Form. A copy of the form with instructions can be found in the appendix of the MITS Procedure SOP.

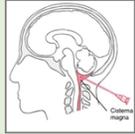
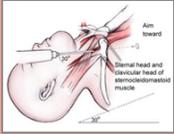
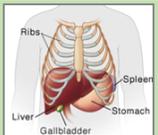
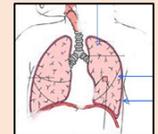
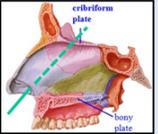
<p>1. Prepare the body and verify the identity</p> <p>2. Anthropometric measurements: weight, body length (use wooden length board), MUAC, head circumference, lower leg length and foot length. Check for bilateral pitting edema</p> <p>3. Inspect and palpate the body: malformations, tumors, skin lesions. Palpate the abdomen and cervical, supraclavicular, axillar, or inguinal nodes</p> <p>4. Photos: Front, back, side, nails, and any lesions (if present). Include label in photos</p> <p>5. Clean and sterilize the body (areas to be punctured): water, alcohol 5 minutes, iodine solution 5 minutes</p>						
<p>6. Cerebrospinal fluid: Middle line below the occipital bone between the squama and atlas bone</p> 	<p>7. Blood: Supraclavicular punctures (mid-way between the sternal notch and acromioclavicular joint)</p> 	<p>8. Stool: Insert the brush 3 to 4 cm into the rectum and rotate</p> 				
<p>9. Nasopharyngeal secretion (not in stillbirths): Insert swab into the nostril and rotate it several times</p> 	<p>Bard Monopty 16 G (n° 1)</p> 		<p>10. Liver and abdominal samples (cryovials and formalin jars #1 and #2): Puncture in the mid-axillary line, one of the three last intercostal spaces</p>			
<p>11. Right thorax for microbiology (cryovials #3 and #4): Upper right mid-axillary thoracic region</p>	<p>12. Left thorax for microbiology (cryovials #5 and #6): Upper left mid-axillary thoracic region</p>	<p>13. Right and left thorax for DNA extraction and PCR (cryovials #14)</p>	<p>14. Right thorax for histology (formalin jars #3 and #4)</p>	<p>15. Left thorax for histology (formalin jars #5 and #6)</p>	<p>Bard Monopty 16 G (n° 2)</p> 	
<p>16. Brain (occipital and fontanelle) for microbiology (cryovials #7 and #8)</p>	<p>17. Brain (transnasal for microbiology) (cryovials #9 and #10)</p>		<p>BIOMOL 16 G Menghini Type</p>	<p>18. Brain (occipital and fontanelle) for microbiology (formalin jars #7 and #8)</p>	<p>19. Brain (transnasal for microbiology) (formalin jars #9 and #10)</p>	
<p>20. Placenta and membranes for microbiology (cryovials #11 and #12)</p>	<p>21. Complete placenta evaluation after 4-24 hours of formalin fixation: Collect histology samples</p>			<p>23. End of the procedure:</p> <ul style="list-style-type: none"> • Complete the MITS Specimen Collection Form • Non-used tools to back-up box • Unused labels pack with collected MITS specimens • All used materials to bio-waste bin • Send all jars and cryovials to the laboratory 		

Figure 5: Provides an illustrative summary of the tissue and non-tissue specimens collected during the MITS procedure.

Several features and updates to the MITS Procedure SOP are noteworthy:

- The following updates were made to the anthropomorphic measurements procedure section (**Section 8.3 of the MITS Procedure SOP**): a wooden length board is used to measure body length; the mid-upper arm circumference (MUAC) is taken from the left arm; head circumference is taken as described in the previous version of the SOP; lower leg length is taken from the right leg and foot length is taken from heel to the longest toe on the right foot. For additional information on using the wooden length board and a checklist see the **MITS Procedure SOP Appendix**.
- A section on Placenta Evaluation (**Section 9.0 of the MITS Procedure SOP**) was added to the MITS Procedure SOP. The section applies to stillbirth or early neonatal MITS cases where placenta is available. The Placenta Evaluation section describes the order of operation for handling placenta and umbilical cord starting from photographing, describing the umbilical cord and membranes, collecting qualitative data, performing serial sections, identifying and describing lesions, collecting cord, membranes and

placental disk specimens, and ending the procedure. The Placenta Gross Examination Form is used to record quantitative and observational data during the placenta evaluation.

- The SOP describes differences in procedures and specimens collected depending on the age of the deceased:
 - Different scales may be used to weigh stillbirths and neonates versus children; if weight for stillbirths and neonates is obtained in grams, convert to kilograms to record on the MITS Specimen Collection Form.
 - Collecting microbiology specimens of the placenta is performed for stillbirths MITS cases only.
 - In some cases, especially stillbirths and neonates, the amount of blood that can be collected is minimal and needs to be prioritized, as described in **Section 8.9 of the MITS Procedure SOP** for culture (1.5 mL) first, followed by EDTA vacutainer (0.5 mL) and filter paper (dried blood spot (DBS)).
 - For brain tissue collection using the fontanelle approach, the posterior fontanelle can only be punctured in infants younger than 3-4 months and the anterior fontanelle in children younger than 12-18 months.
- Based on results, the routine collection of bone marrow samples from infants and children is no longer required and will be performed only when deemed necessary based on clinical information (**see Retired Specimen Collection in the MITS Procedure SOP appendix**).

The following materials are in the MITS Procedure SOP appendix and are explained briefly below:

- a. Specimen Collection Kit Components
- b. Retired Specimen Collection
- c. Anthropometry: A Checklist: Measuring Length of Children in the Postmortem Setting
- d. Cryovial and Formalin Jar Designations
- e. Job-Aid for Using the Supplied Labels
- f. Disposition of Body Form (CRF 06.01.04) with instructions
- g. MITS Specimen Collection Form (CRF 06.02.01) with instructions

a. Specimen Collection Kits

The appendices in the MITS Procedure SOP provides a full list of the items and labels contained in the MITS Specimen Collection Kit. The kit contains all the required tools and labels for performing one MITS procedure. Back-up kits are provided in case additional tools are needed.

b. Retired Specimen Collection

A list of previously collected and no longer collected specimens is available in the MITS Procedure SOP appendix. Bone marrow, hair and urine are currently retired. However, if the specialist suspects one or all the specimens may aid in determining cause of death, steps and illustrations are present in the appendix to aid in the collection.

c. Anthropometry: A Checklist: Measuring Length of Children in the Postmortem Setting

Anthropometric measurements are required for the MITS Procedure. The types of measurements and how to measure are explained in the first sections of the MITS Procedure. If more information is required, a checklist and illustration is provided in the appendix of the MITS Procedure SOP.

d. **Cryovial and Formalin Jar Designations**

The cryovial and formalin jar designations identify tissues that will be frozen and formalin-fixed. The container labels on both frozen and formalin-fixed tissue dictate where the tissue will be sent (i.e., site storage versus biorepository and site pathology laboratory versus CPL).

e. **Job-Aid for Using the Supplied Labels**

The Job-Aid is intended to assist with the performance of the procedure, ensure correct identification and labeling of specimens and containers.

f. **Disposition of Body Form (CRF 06.01.04)**

A copy of CRF 06.01.04 with instructions is in the appendix of the MITS Procedure SOP. The instructions aid in the complete and accurate entry of data during the MITS procedure.

g. **MITS Specimen Collection Form (CRF 06.02.01)**

A copy of CRF 06.02.01 with instructions is in the appendix of the MITS Procedure SOP. The instructions aid in the complete and accurate entry of data during the MITS procedure.

MITS Specimen Collection Form (CRF 06.02.01)

The MITS Specimen Collection Form captures the quantitative and observational data during the MITS procedure. During the MITS procedure following each step, the assistant notes the collection of the specimen and any additional comments or notes from the specialist.

Placenta Gross Examination Form (CRF 07.00.13)

The Placenta Gross Examination Form records the pathologist's macroscopic observations, measurements, and areas of the placenta and umbilical cord sampled for histology purposes.

Note: *The Placenta Gross Examination can be completed on fresh placenta or after the placenta has been fixed and sent to the pathology laboratory. The Placenta Gross Examination form is also mentioned in the **Clinical Diagnostics** section along with the Placenta Microscopic Examination form.*

2. Specimen Accessioning and Distribution

Following the MITS procedure, specimens are brought to the local site laboratory for accessioning and distribution. Tissue specimens for both the local histology laboratory and the CPL are fixed in formalin for 4-24 hours prior to transferring to 70% alcohol. Non-tissue specimens are aliquoted and distributed for culture, TAC assay, Malaria (thick, thin smears and Rapid Diagnostic Tests (RDTs)), TB (GeneXpert), and HIV testing. In addition, QA aliquots are taken for the Central Biorepository (CBR) and/or retesting. Specimens are either stored at the site storage or sent to CBR.

The SOPs, forms and guidance documents described in this section provide specific instructions and quality-related comments/notes that are used to guide CHAMPS site personnel during the accessioning, distributing, shipping and storing of specimens. CHAMPS site personnel should note appropriate temperatures for handling and storing specimens and document any deviations.

A. Standard Operating Procedures and Forms

The following provides a brief overview of the SOPs, forms and guidance documents ([see Master List of Standard Operating Procedures, Forms, and Other Documentation](#)) related to the specimen accessioning, shipping and storage.

Specimen Accessioning and Distribution SOP (07.00.01)

The Specimen Accessioning and Distribution SOP describes the steps for accessioning and distributing tissue and non-tissue specimens collected during the MITS procedure. The SOP details how tissue and non-tissue specimens are transported following the MITS procedure, aliquoted, distributed and prepared for testing or shipping (see **Figure 6**). The SOP appendix contains images showing and step-by-step instructions describing how to transfer tissue specimens to cassettes to prevent loss during transport and shipping.

International Shipment of Specimens SOP (07.04.03)

The International Shipment of Specimens SOP describes the procedures for shipping the CHAMPS formalin-fixed tissue specimens for evaluation by the CPL and shipping the frozen tissue and non-tissue specimens to the biorepository. The SOP details the shipping container set-up, temperature conditions, paperwork submission to World Courier and CHAMPS PO; required labels; and permit when shipping specimens.

Biorepository SOP (07.04.02)

The Biorepository SOP describes procedures for the storage and management of CHAMPS specimens. The SOP describes the steps for handling, shipping, storing, maintaining inventory control, reporting and auditing the frozen specimen collection. In addition, the SOP provides general guidance and best practices for specimen storage and biorepository operations.

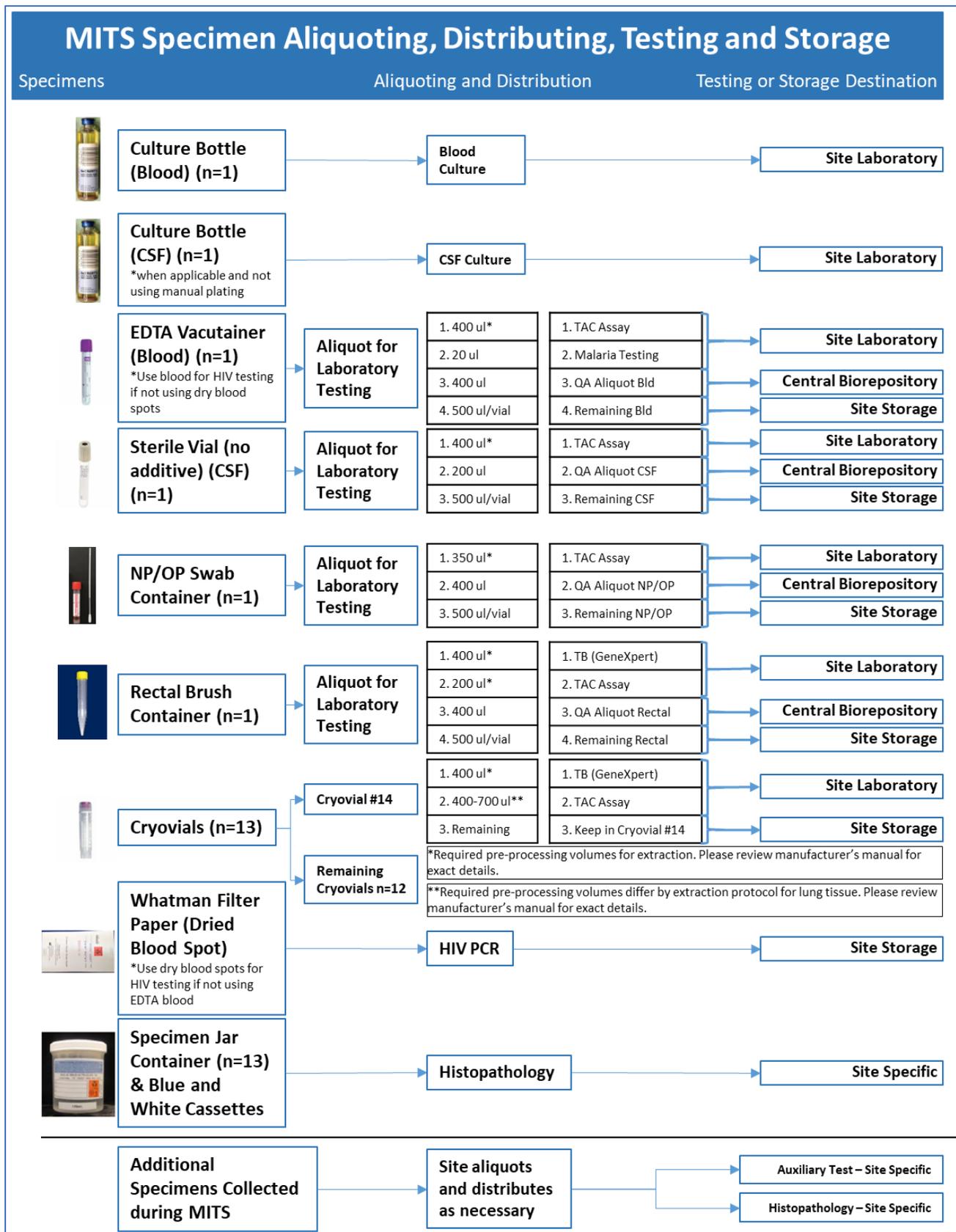


Figure 6: High-level diagram illustrating aliquoting, distributing, testing and storage of non-tissue and tissue specimens collected during the MITS procedure.

To maintain specimen integrity following the MITS procedure, specimens should be transported in properly labeled, sealed vials and containers, and should be kept at appropriate temperatures for the given specimen type (see **Table 2**).

Specimen	Container	Transportation condition
CSF	T-I media bottle in candle jar	Room temperature
Tissue	Formalin jars	
DBS	Whatman Filter paper	
CSF	Sterile vial	Cool Box (2-8°C)
Blood	Blood culture bottle	
Blood	EDTA vacutainer	
NP swab	Cryovial	
Rectal swab	Cryovial	
Tissue	Cassettes	
Tissue	Cryovials	Dry Shipper

Table 2: Preferred transportation conditions for tissue and non-tissue specimens when transporting specimens for greater than 1 hour.

B. Timeline (Start to Finish)

Full pathology analysis on most cases will be completed within 4-8 weeks after tissues are received at CPL. The extended range represents the additional time required in some challenging cases or unexpected issues which might slow review. If tissues can be shipped and received within 3 weeks after death, and that CPL histopathology and all other clinical, epidemiological and VA data are made available within 10-11 weeks after death, a definitive cause of death can be assigned within 3 months after the death. If shipping delays occur and/or additional time is required for testing at CPL, the cause of death determination may extend to 4 months after death.

3. Clinical Diagnostics

After MITS specimen collection, tissue and non-tissue specimens are distributed to the site laboratory for microbiology culture, molecular testing, and histology and additional tissue specimens are shipped to the CPL for histology, Special Stains (SS), and IHC. The first two sections below describe non-tissue and tissue specimen testing. The third section provides brief explanations for all the SOPs and forms used for tissue and non-tissue processing, testing and reporting.

A. Non-Tissue Specimen Testing

Non-tissue specimens collected during the MITS procedure and tested at the site laboratory include blood, cerebrospinal fluid (CSF), NP swab, and stool/rectal swab. The testing of non-tissue specimens is summarized in **Table 3** and include bacterial culture specific assays for HIV, TB, malaria, and for an array of pathogens utilizing the TAC assay (for additional information on the TAC assay, see [TaqMan Array Cards \(TAC\)](#)).

Specimen Collected	CHAMPS Diagnostic Testing
Blood	Microbiology (Culture, Gram Stain), HIV PCR (DBS), Malaria (thick and thin smears, RDT), TAC
CSF	Microbiology (Culture, Gram Stain), TAC
NP swab	TAC
Stool/Rectal swab	TAC, GeneXpert TB

Table 3: Non-tissue specimens and diagnostic testing

Cultures and Isolates

Standard methodologies are available for performing microbiology cultures, Gram stain and isolate identification. Sites should select the testing methods based on expert recommendations, geographic location and available resources.

HIV, Malaria and TB Testing

There are many standardized types methodologies for detecting HIV, malaria and TB in the MITS collected specimens. For detecting HIV nucleic acids (DNA or RNA) from DBS or whole blood, the following molecular systems can be used COBAS AmpliPrep/Cobas TaqMan HIV-1 v2.0 testing technology (Roach Molecular Systems), Abbott Molecular m2000 Real-time System for HIV-1, or comparable existing molecular system. For TB testing, GeneXpert is a standardized molecular TB test that can give a result in less than 2 hours using real time polymerase chain reaction technique. The technology is currently used at all sites to test stool/rectal swab for the presence of TB and rifampin resistance (*rpoB*) gene. For malaria testing, thick and thin smears are standardized methodologies for determining the number of parasites present in blood (% infected red blood cells or parasites/ μ l). In addition, sites employ any one of the appropriate Malaria RDTs for their region (see [Malaria RDT Product Testing — Interactive Guide](#) for additional information on RDTs). Sites should select the rapid testing methods based on expert recommendations, geographic location and available resources.

Specimen Preparation and Quality (Technical)

Blood in culture bottle should be transported to the site laboratory (with emphasis on maintaining an optimal temperature range) and placed in instrument as soon as possible and ideally within 4- 8 hours from time of blood collection.

Depending on the final volume of blood obtained, the following tests will be prioritized. The priority for blood specimen testing is as follows:

- Culture (1.5 ml)
- TAC assay (0.5 ml)
- Malaria (0.1 ml)
- HIV (0.1 ml)
- Aliquot for storage/future analyses (e.g., metagenomics)
- Serum separation

B. Tissue Specimen Testing

Tissue specimens collected during the MITS procedure, excluding the majority of the frozen tissue specimens, are prepared for the TAC assay and histopathology evaluation (see **Table 4**).

Specimen Collected	CHAMPS Diagnostic Testing
Liver/Abdominal Organs	Histology
Left and Right Thorax	TAC, GeneXpert TB, Histology
CNS – Post-nasal	Histology
CNS – Posterior and Fontanelles	Histology
Placenta/Cord	Histology

Table 4: Tissue specimens and diagnostic testing

All formalin-fixed tissue specimens (including placenta and umbilical cord) sent to the site pathology laboratory and the CPL are processed and embedded (Tissue Processing SOP), sectioned (Tissue Sectioning SOP) and H&E stained (H&E Staining SOP). Following histopathology evaluation, CPL and if capacity allows, the sites, conduct special staining (Special Stains SOP) and/or IHC testing (IHC Testing SOP). Both the site and CPL independently evaluate all tissue specimens and record findings separately in the Site Pathology Report Form and the CPL Pathology Report.

The fresh tissue specimens, collected in cryovials, are frozen and prepared for either the site storage location or shipment to the biorepository (see International Shipment of Specimens SOP). Future microbiology or other testing may be conducted on frozen tissue specimens depending on clinical laboratory results and histopathology evaluation. Cryovial 14 containing left and right thorax tissue is used for TB and rifampin resistance using GeneXpert and nucleic acid (NA) extraction for TAC assay (see Tissue Extraction SOP in the [TaqMan Array Cards \(TAC\)](#)).

Approach for Infectious Disease Testing in Tissue Specimens

For histopathology examination, pathogens are not defined prior to microscopic examination. The pathologists use a syndromic approach based on histopathologic patterns of disease (infectious and non-infectious) to determine which etiologies to look for and assays to perform. The algorithms start with histopathologic findings compatible with a particular syndrome; orders for tests proceed from less specific methods (i.e., SS to identify presence of bacteria, fungi, etc.) to more specific methods (i.e., IHC for specific pathogens or groups of pathogens). **Figures 7-11** describe the infectious disease algorithms for determining bronchopneumonia, interstitial pneumonia, meningitis/meningoencephalitis, sepsis, as well as aspiration in stillbirths and early neonates [11].

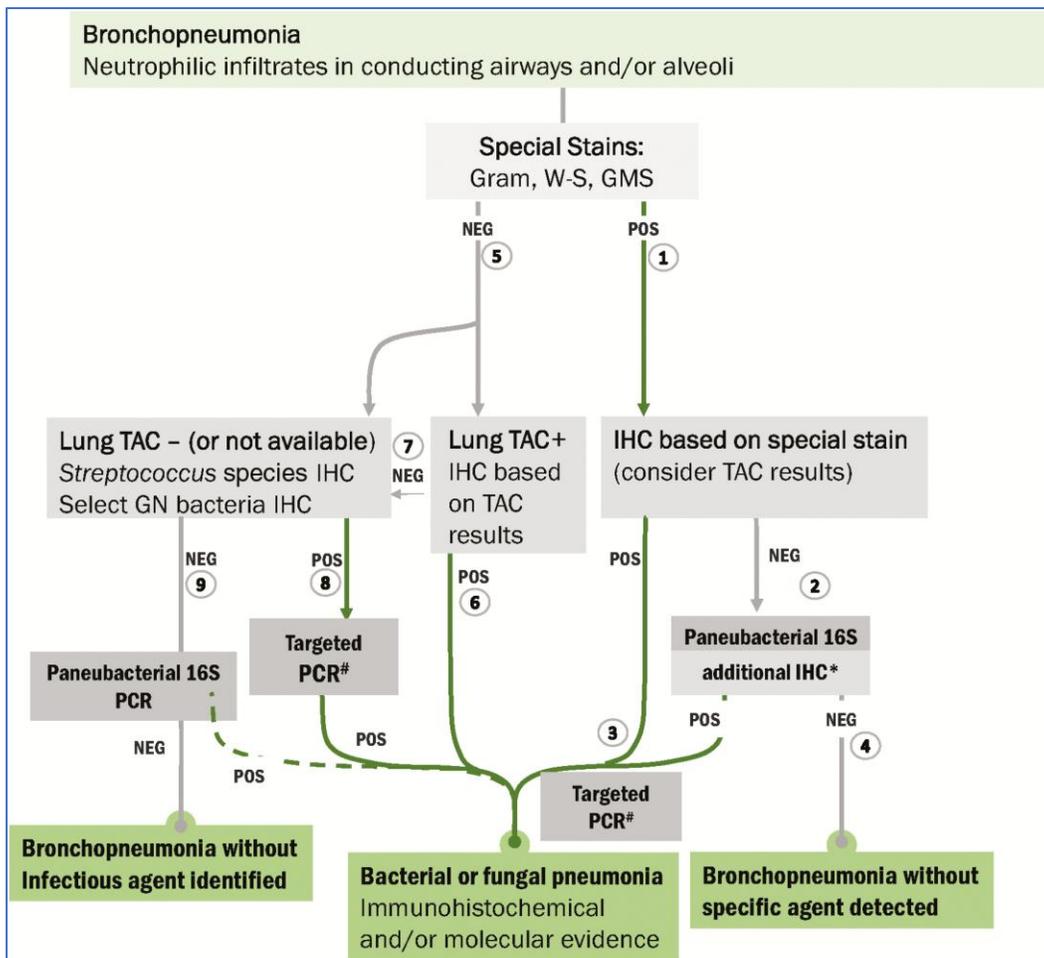


Figure 7. Algorithm for evaluation of bronchopneumonia in MITS from children U5. Bronchopneumonia is characterized by neutrophilic infiltrates within air spaces and prompts performing SS (Gram, Warthin-Starry [W-S], Grocott methenamine silver [GMS]) to evaluate for bacteria or, less commonly, other agents such as fungi. If SS are positive (POS) (right side of algorithm) (1), IHC is performed for relevant agents with compatible morphology and SS characteristics seen. (Agents detected on lung TAC with compatible features seen by SS should be included in IHC testing.) If these SS and TAC-guided IHC are negative (2), paneubacterial 16S polymerase chain reaction (PCR) with sequencing and additional IHC testing (*) to include *Streptococcus* species and select Gram-negative (GN) bacteria are performed on the formalin-fixed, paraffin-embedded (FFPE) tissue. (Select GN bacterial IHC assay uses an antibody raised against *Klebsiella pneumoniae* but is also known to detect *Escherichia coli*, *Haemophilus influenzae*, and *Pseudomonas* species, among others. Immunostaining with this antibody is interpreted in conjunction with results of other tests [ie, TAC, FFPE-based PCR, cultures] to identify a specific agent.) At either point when POS IHC results are obtained (3), targeted PCR is performed for further identification when available, and a final diagnosis of agent-specific pneumonia is made when possible. If an etiologic agent is not identified by IHC or PCR testing (4), a diagnosis of “bronchopneumonia with no agent detected” is made. If SS are negative (NEG) (left side of algorithm) (5), IHC is performed for any potentially relevant agents detected in lung TAC; POS IHC results (6) confirm agent-specific pneumonia. If no agents are detected on lung TAC or TAC results are not available, or if IHC for agents detected in lung TAC is negative (7), then screening by IHC for *Streptococcus* species and select GN bacteria is performed. If POS (8), targeted PCR is performed for further identification and a diagnosis of agent-specific pneumonia is made. If *Streptococcus* species and select GN bacterial IHC is negative (9), then paneubacterial 16S PCR is performed as needed to attempt bacterial identification. #Targeted PCR is performed when available.

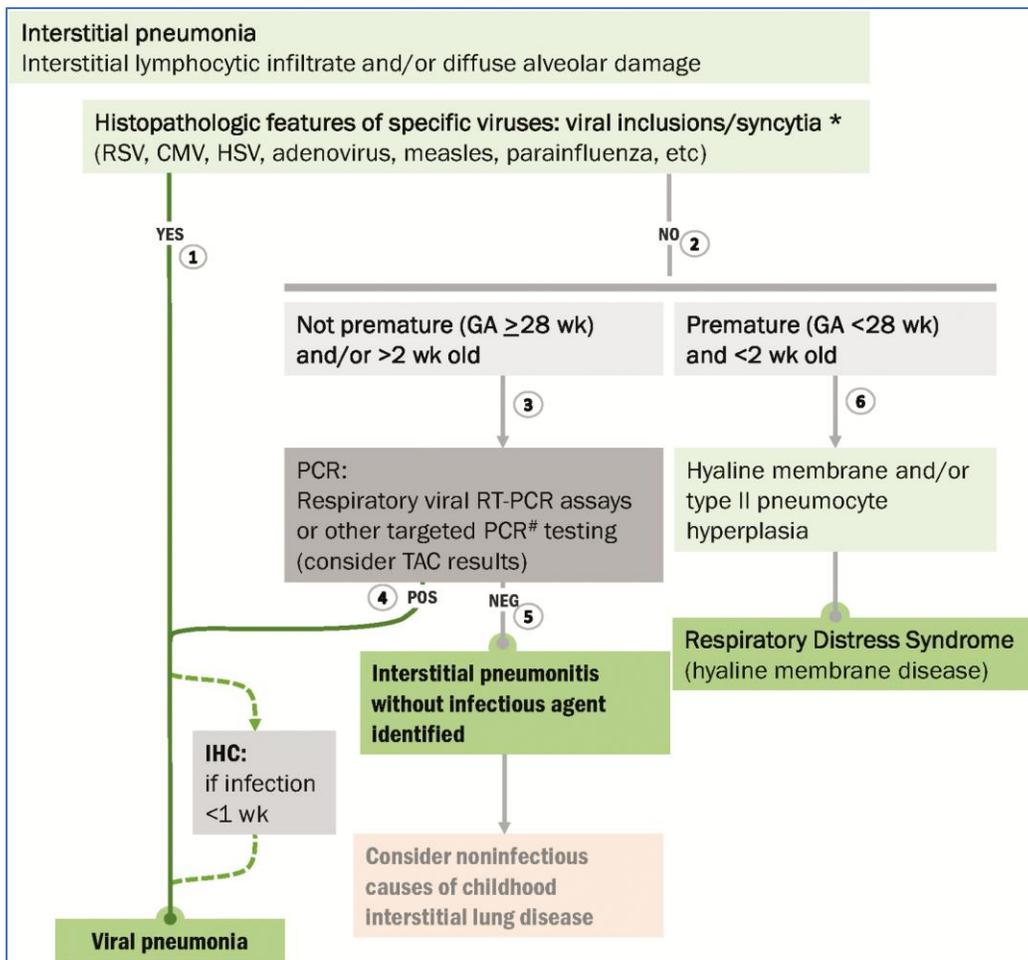


Figure 8. Algorithm for evaluation of infectious etiology in lungs with interstitial pneumonia in MITS from children US. Interstitial pneumonia is characterized by lymphocytic interstitial lymphocytes and/or diffuse alveolar damage (hyaline membranes, type II pneumocyte hyperplasia) and prompts evaluation for primarily viral etiologies in infants >2 weeks. (*Some causes of bacterial sepsis, particularly *Neisseria meningitidis*, should also be considered in cases of lymphocytic interstitial pneumonitis.) If histopathologic features of specific viruses (e.g., characteristic viral inclusions or syncytia) are seen (1), then a diagnosis of agent-specific viral pneumonia is made. If clinical history indicates duration of illness <1 week, IHC may be performed for further confirmation. If features of a specific virus are not seen (2), then age at death and gestational age (GA) at birth are critical to further interpretation of lung findings. If the infant was >2 weeks old at death, and GA at birth was >28 weeks (3), PCR testing for respiratory viruses (influenza A/B, parainfluenza viruses 1–4, and respiratory syncytial virus (RSV)) is performed on the FFPE tissue. Detection of other respiratory viruses in lung TAC should prompt testing for those agents. Positive PCR leads to a diagnosis of agent-specific viral pneumonia (4), whereas NEG PCR (5) results in a diagnosis of interstitial pneumonitis without infectious agent identified and consideration of noninfectious causes of childhood interstitial lung disease. If the infant was <2 weeks old at the time of death, and GA at birth was <28 weeks (6), the presence of hyaline membranes, with or without type II pneumocyte hyperplasia, is compatible with a diagnosis of infant respiratory distress syndrome (hyaline membrane disease). #Targeted PCR is performed when available.

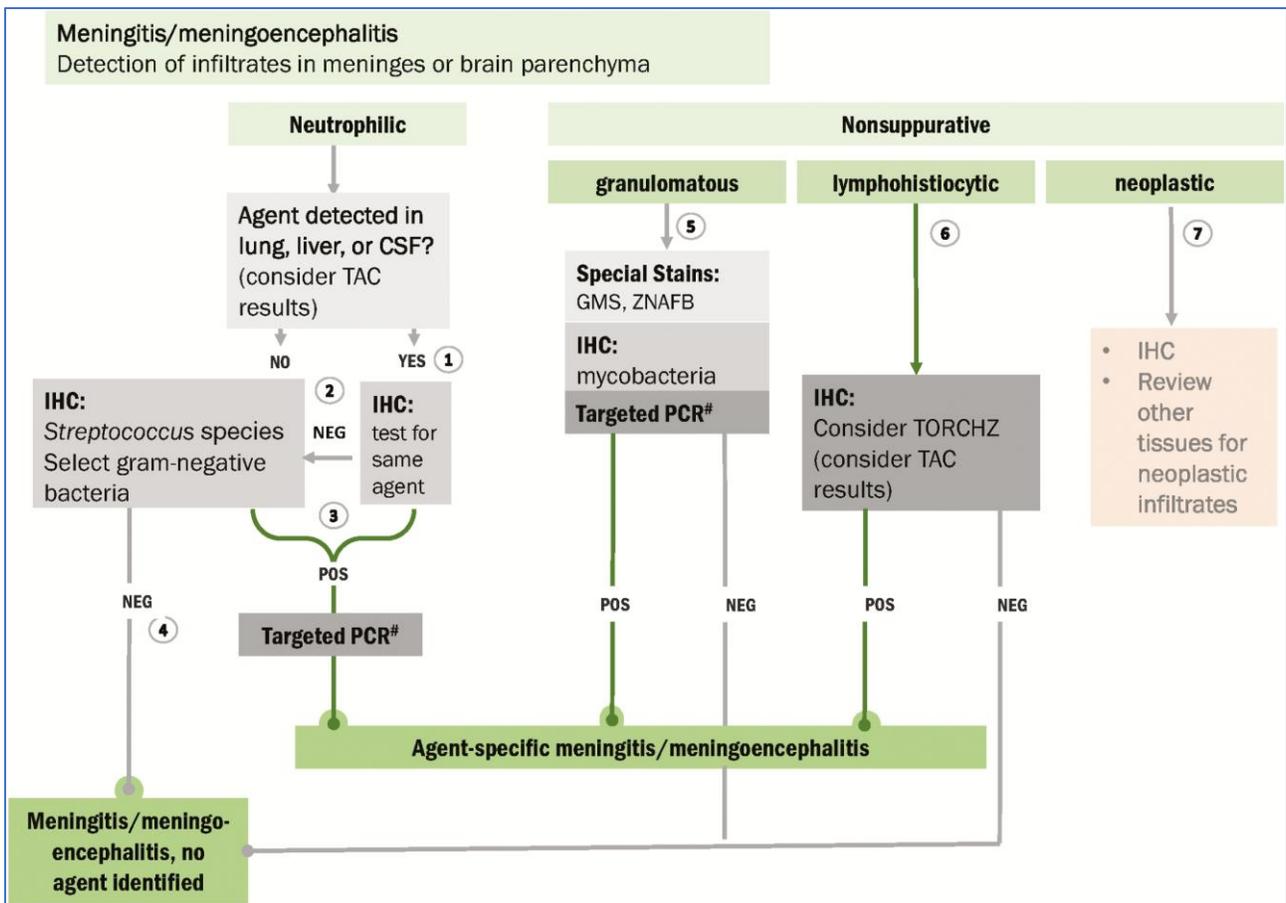


Figure 9. Algorithm for evaluation of brain samples with histopathologic diagnosis of meningitis or meningoencephalitis in MITS from children U5. Meningitis and meningoencephalitis are characterized by detection of cellular infiltrates in the meninges and brain parenchyma, and the character of the infiltrate directs diagnostic testing. Neutrophilic infiltrates prompt consideration of primarily bacterial etiologies, and initial IHC testing should be performed for agents detected in other tissues (lung, liver, CSF, blood) by IHC or TAC (1). Strong consideration should be given to agents detected in CSF by TAC. If agents are not detected in other tissues or CSF TAC is NEG or not available, or if agents detected in CSF TAC are NEG by IHC (2), then screening by IHC for *Streptococcus* species and select GN bacteria is performed. If at any point POS IHC results are obtained (3), targeted PCR assays are performed on the FFPE tissue for further identification and a diagnosis of agent-specific meningitis/meningoencephalitis is made when possible. If an agent is not detected by IHC (4), the diagnosis is meningitis/meningoencephalitis, no agent identified. Nonsuppurative infiltrates warrant testing for other bacteria and nonbacterial agents, or consideration of neoplasia. Granulomatous infiltrates (5) direct to testing by SS, IHC, and/or PCR for mycobacteria and fungi, whereas lymphoplasmacytic infiltrates (6) prompt more consideration of viral and protozoal agents (especially *Toxoplasma*, rubella, CMV, HSV, *Treponema*, and Zika). Cellular infiltrates with features of neoplasia (7) should be characterized by appropriate IHC if warranted and available, and other tissues reviewed for evidence of neoplasia. #Targeted PCR is performed when available.

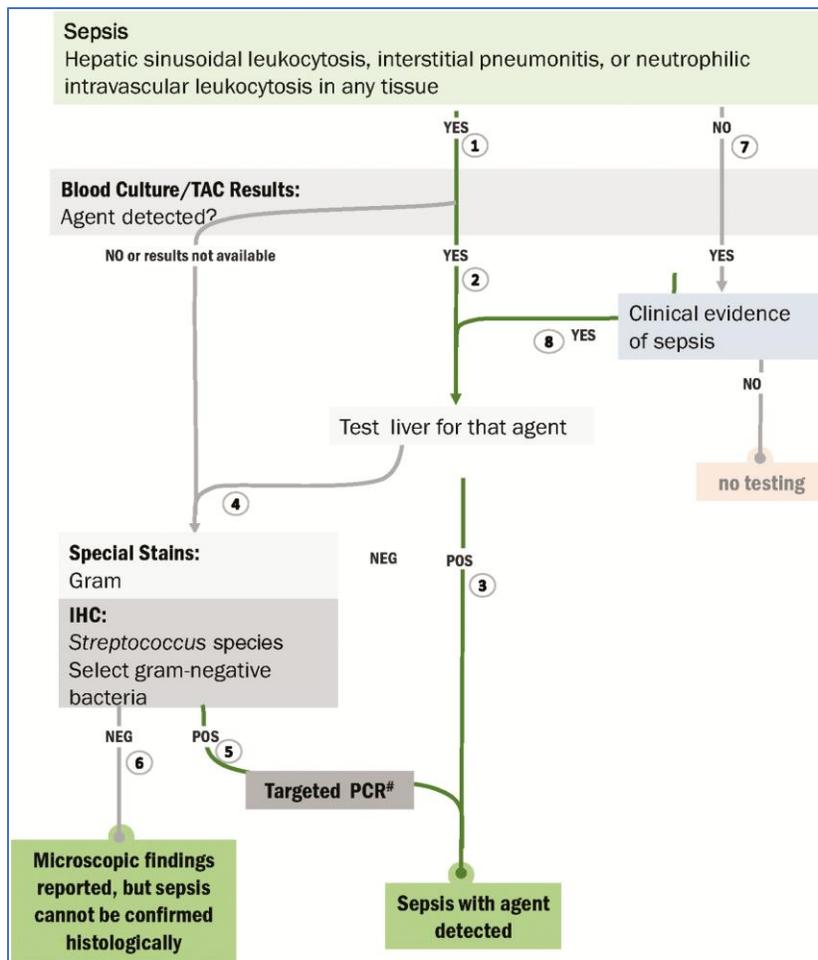


Figure 10. Algorithm for evaluation of tissue samples with histopathologic diagnosis of sepsis or clinical and laboratory suspicion of sepsis in MITS specimens from children U5. Histopathologic features of sepsis in MITS samples include hepatic sinusoidal leukocytosis, acute interstitial pneumonitis, or neutrophilic intravascular leukocytosis in any tissue. If these features are seen (left side of algorithm) (1), then IHC testing should be performed on liver and other tissues with histopathologic features of sepsis for agent(s) detected on blood culture and/or TAC, if available (2). POS IHC results confirm sepsis due to that agent (3). If blood culture and TAC results are negative (NEG) or not provided, or if IHC testing for agents detected by blood culture/TAC are negative (4), screening by Gram stain and IHC for *Streptococcus* species and select GN bacteria are performed. If IHC is POS (5), targeted PCR assays for identification of agent and/or further speciation are performed. If an agent is not confirmed by IHC (6), the diagnosis is limited to the histopathologic features observed (e.g., hepatic sinusoidal leukocytosis, intravascular leukocytosis); a diagnosis of sepsis is not made unless bacteria are demonstrated by IHC. If histopathologic features of sepsis are not present in any tissue, but a relevant agent is detected on blood culture and/or TAC (7), correlation with clinical features is recommended and then testing of liver by IHC for that agent is performed only if the clinical history is compatible with known or suspected sepsis (8). #Targeted PCR is performed when available.

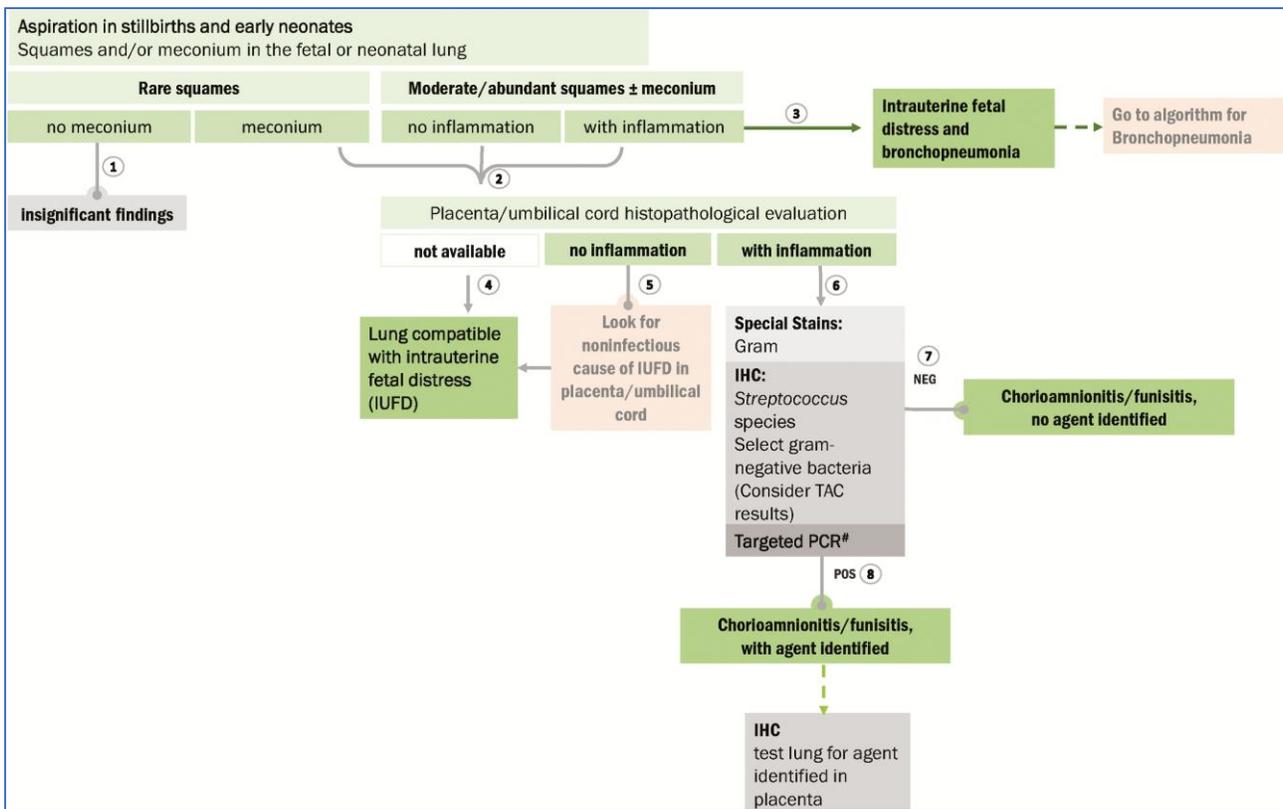


Figure 11. Algorithm for evaluation of aspiration in stillbirths or early neonates in MITS from children U5. The presence of squames and/or meconium in the lungs of stillbirths or neonates indicates in utero amniotic fluid aspiration and warrants special consideration of potential causes, including placental evaluation for evidence of in utero infection or placental abnormalities. The presence of only rare squames without meconium is considered an insignificant finding (1), whereas the presence of moderate or abundant squames, and any amount of meconium, indicates intrauterine fetal distress (IUFD) and prompts evaluation of placental and umbilical cord tissues (2). If neutrophilic inflammation accompanies squames/meconium in the lung (3), the bronchopneumonia algorithm (**Figure 7**) should also be initiated to investigate for infectious etiologies. If placenta and umbilical cord are not available (4), then the diagnosis is limited to IUFD. If placenta and umbilical cord have no inflammation (5), they are evaluated for potential noninfectious causes of IUFD (e.g., placental infarct). If these tissues do have inflammation (6), evaluation for infectious agents by SS and IHC are performed for *Streptococcus* species and select GN bacteria. Agents detected on lung, blood, or CSF TAC should be prioritized for testing in the placenta. If agents are not identified (7), a diagnosis of chorioamnionitis/funisitis, no agent identified is made. If an agent is identified (8), the agent associated with chorioamnionitis/funisitis should also be tested for in the lung tissue. #Targeted PCR is performed when available.

C. Standard Operating Procedures and Forms

The documentation listed below briefly explains the SOPs, forms and manuals (see [Master List of Standard Operating Procedures, Forms, and Other Documentation](#)) used for testing specimens and reporting results. The hyperlinked forms (see [Forms](#)) contain instructions for accurately and completely recording data.

Tissue Processing SOP (07.02.01)

The Tissue Processing SOP describes the steps for processing and embedding tissue for histopathology evaluation.

Note: *The SOP contains steps and times for both manual and automated tissue processing.*

Tissue Sectioning SOP (07.02.02)

The Tissue Sectioning SOP describes microtome and water bath set up, facing paraffin blocks, sectioning 4 µm sections and collecting sections on glass slides.

H&E Staining SOP (07.02.03)

The H&E Staining SOP describes the steps for deparaffinizing, hydrating and staining tissue with hematoxylin and eosin.

Special Stains SOP (07.02.04)

The SS SOP describes deparaffinizing, hydrating and staining with the following stains; Gram, Periodic Acid Schiff (PAS), and Acid-Fast Bacilli (AFB). Gram staining stains and differentiates Gram-positive and Gram-negative bacteria. The PAS stains carbohydrate rich cells, this includes macrophages, connective tissue and fungi. The AFB stain, also known as Ziehl-Neelsen stain, differentiates between acid-fast and non-acid fast bacteria, which is useful for differentiating acid-fast bacteria such as *Mycobacterium*.

Immunohistochemistry Testing SOP (07.02.0X) [In Development]

The IHC Testing SOP describes the steps for performing IHC and available commercial antibodies.

For all forms listed below, instructions have been added to the forms to aid in accurate and complete data entry (see [Forms](#)).

Clinical Lab Results Form (CRF 07.00.03)

The Clinical Lab Results Form records clinical laboratory results for malaria, HIV, TB, and any auxiliary tests.

Blood Microbiology Results Form (CRF 07.00.04)

The Blood Microbiology Results Form records microbiology results from blood and CSF cultures, Gram staining, isolate testing, and organism identification.

Lung Microbiology Results Form (CRF 07.00.12)

The Lung Microbiology Results Form records microbiology results from lung tissue, Gram staining, isolate testing, and organism identification.

Note: Reporting lung microbiology results is not mandatory if site is currently not performing testing.

Gross Examination Form (CRF 07.00.09)

The Gross Examination Form records measurements of formalin-fixed tissues sent to the site pathology laboratory and the CPL.

Placenta Gross Examination Form (CRF 07.00.13)

The Placenta Gross Examination Form records the site pathologist's macroscopic observations, measurements, and areas of the placenta and umbilical cord that are sampled for histology purposes.

Placenta Microscopic Examination Form (CRF 07.00.14)

The Placenta Microscopic Examination Form records the site pathologist's microscopic observations and findings for the umbilical cord, membranes, and placental disk

Site Pathology Report Form (CRF 07.00.05)

The Site Pathology Report Form records the site pathologist's observations and findings of tissue processed for histopathology, including whether the tissue is technically adequate (i.e., tissue and processing quality), the correct tissue is present in the block, and the presence of pathogens and/or specific pathology.

Note: *Only complete the Placenta and Cord (Cassette F) portion of the form if placenta was collected under the old MITS protocol otherwise, complete Placenta Microscopic Examination Form (CRF 07.00.14).*

CPL Pathology Report [submitted as a PDF not as RedCap form]

The CPL Pathology Report records the CPL pathologist's observations and findings of tissue processed for histopathology, SS, and IHC, including whether the tissue is technically adequate (i.e., tissue and processing quality), the correct tissue is present in the block, and the presence of pathogens and/or specific pathology.

Manufacturer's Manuals

Various technologies/equipment are used for testing tissue and non-tissue specimens at sites, the CHAMPS PO recommends referring to the manufacturer's manuals for questions, troubleshooting, interpretation and training purposes.

Note: *Refer to section 4 for TaqMan Assay Card (TAC) related information.*

4. TaqMan Array Cards (TAC)

This section provides an overview of the TaqMan Array Card (TAC) assay testing utilizing NA extracted from blood, CSF, nasopharyngeal (NP) swabs, stool/rectal swab and lung tissue specimens collected during the MITS procedure. The four specifically designed CHAMP TAC cards test for the molecular presence of up to 120 different pathogens (for a full list see TAC Assay Appendix SOP). In addition to providing steps for extracting NA and running the TAC cards, the documentation described below provides critical information for handling and storing specimens and extracted NA; interpreting, analyzing, and reporting TAC results; and practicing safe laboratory procedures.

TAC cards were designed in consultation with external scientific advisors; multiplexing within wells have been planned to accommodate additional pathogens. All newly developed real-time PCR assays are evaluated using individual RT-qPCR reactions prior to use on the TAC format. The limit of detection is independently determined for each assay by testing at least 3 replicates of each of a 10-fold dilution series total NA ranging from 0.1 fg/ul to 1 ng/ul. Inclusivity is assessed by testing representative isolates, including various subspecies, serotypes, or clonal groups as appropriate. Specificity of each assay is assessed by testing 15 ng of NA from at least 200 different bacteria, viruses, protozoa, or fungi. Validation of new TAC cards on clinical samples will take place at selected sites and then expanded.

The SOPs, forms and guidance documents described in this section provide specific instructions and quality-related comments/notes that are used to guide CHAMPS site personnel as they extract NA, perform TAC assays, conduct analysis and submit results. CHAMPS site personnel should note appropriate temperatures and conditions for handling, testing and storing specimens and document any deviations.

A. Standard Operating Procedures and Forms

The following provides a brief overview of the TAC SOPs, forms and guidance documents. For further clarification on any of the items mentioned below or technical details, all SOPs and forms can be found in the [Master List of Standard Operating Procedures, Forms, and Other Documentation](#).

Nucleic Acid Extraction SOPs

To obtain NA for the TAC testing, the following SOPs detail steps, handling, and conditions to ensure standardized treatment, inactivation and extraction of NA: Blood and CSF Specimens Extraction SOP (07.01.02.01), Respiratory Specimens Extraction SOP (07.01.02.02), Stool/Rectal Swab Specimens Extraction SOP (07.01.02.03), and Tissue Specimens SOP (07.01.02.04).

Specific items to note from the extraction SOPs:

- For the blood and CSF specimens, 400 µL of each respective specimen is required. If available volume of specimens is less than 400 µL, add as much specimen volume as available and make up the remaining volume with an appropriate buffer.
- For the respiratory secretion specimens, 350 µL is required. If there is not 350 µL, add as much specimen volume as available and make up the remaining volume with an appropriate buffer.
- For the rectal swab/stool specimen, the specimen is re-suspended/rehydrated in an appropriate buffer. A volume of 200 µL of specimen is required for inactivation and lysis. A 400 µL aliquot of inactivated and lysed stool/rectal swab specimen undergoes NA extraction and then TB (GeneXpert) testing. In addition, a 200 µL of inactivated and lysed stool/rectal swab specimen undergoes NA extraction.

- For the tissue specimen extraction, the tissue specimen should be extracted on the same day it arrives in the laboratory or stored at -70°C and extracted within 72 hours. Following extraction, the NA can be stored at 4°C (if TAC testing will be performed in ≤ 72 hours.) or batched at -70°C until TAC testing. Following specimen inactivation and lysis, a 400 µL undergoes NA extraction for GeneXpert and 400 – 700 µL (depending on the extraction protocol) undergoes NA extraction for TAC assay.
- For all extraction SOPs, the NA extraction output volume should be a minimum of 100 µL to ensure enough NA for TAC testing and repeat TAC testing, if necessary.
- The NA extract can remain at 4°C for up to 72 hours after extraction if the NA will be run over TAC within the 72-hour timeframe; otherwise, the NA should be stored at -70°C until TAC testing is performed.
- Following TAC testing the remaining NA extract should be stored at -70°C.

TaqMan Array Card Testing SOP (07.01.01)

The TaqMan Array Card Testing SOP instructs on proper setup of TAC and operation of ViiA 7 Real-Time PCR System (ViiA7) or Quant Studio 7 Flex (QS7) real-time PCR instruments (see **Figure 12**). TAC, formerly known as TaqMan Low Density Array, is a multiple-pathogen detection system consisting of a 384-well array (see **Figure 13**) of reaction vessels for the amplification of NA using TaqMan real-time polymerase chain reaction (PCR) technology. The wells of the TAC contain specific dried-down primers and hydrolysis probes for the detection of defined pathogen-specific or control targets. Relative levels of amplification directly correlate to the fluorescence data generated and measured during the reaction(s) using the ViiA 7 or QS7 real-time PCR instruments. Fluorescence amplification indicates the presence of the specific NA target.

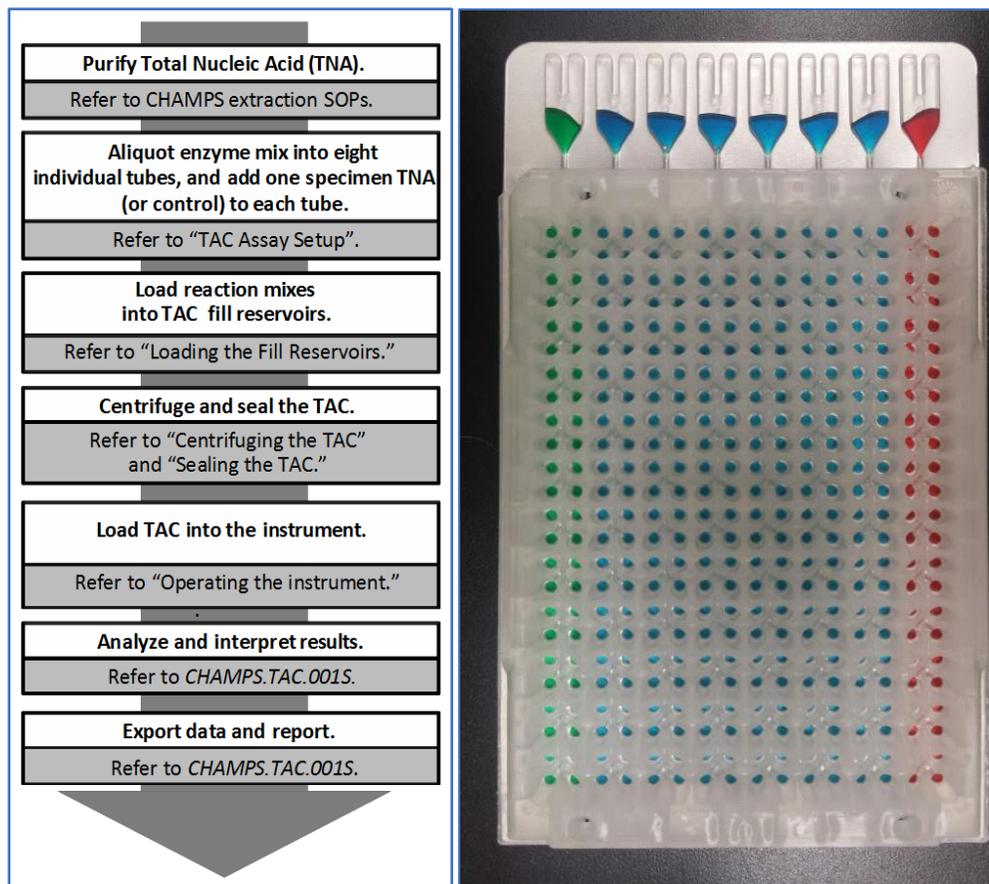


Figure 12: Describes the workflow for the TAC procedure from NA purification to exporting data and reporting.

Figure 13: An image of a TAC after proper centrifugation and sealing. The colors are for illustration purposes. The green corresponds to the “no template control,” the blue corresponds to the six specimen extracts, and the red corresponds to the “positive control.”

Supplemental TAC Analysis SOP (07.01.01.01)

The purpose of this SOP is to serve as a supplemental “how to” TAC analysis document using the QS7 software. The QS7 software (with v1.2 CDC patch) is the real-time PCR software used to analyze TAC results and export the data. The v1.2 CDC enables functionality to assign interpretation for multiplex reactions in the TAC format and ensures that all CHAMPS TAC data across all CHAMPS sites is analyzed in the same format.

TaqMan Array Card Assay Information and Multi-target Interpretation Appendix (TAC Assay Appendix) SOP (07.01.01.02)

The TAC Assay Appendix is composed of four appendices; the first contains a table of possible organisms that are detectable by TAC in addition to cross reactivity, limitations and notes. The second appendix contains multiple target interpretation algorithms. The third identifies assays requiring cutoffs (Ct) and indeterminate comment assigning. The fourth appendix describes each of the four TAC card designs. Finally, the fifth appendix is the TAC laboratory tracking form to capture critical information about each TAC card.

TAC Tracker Form (CRF 07.01.01)

The TAC Tracker Form captures whether the Respiratory (Lung Tissue and NP), Diarrhea (Rectal Swab, Stool), Tier 1 (Blood and CSF) and Tier 2 (Blood and CSF) TAC assay cards were completed with valid results. If one or all the TAC cards were not completed, a reason or reasons must be recorded in the form. In the case of lung tissue, specimen condition must be recorded.

Streptococcus pneumoniae Serotyping

For specimens that are positive for *Streptococcus pneumoniae*, serotype testing is performed using the TAC assay and a separate SPN card. The approach has been standardized across the CHAMPS Network.

TAC Video [In Development]

For training purposes, an instructional video is being developed to aid in TAC assay training. Once developed, information on how to access will be provided.

5. CPL and Telepathology

The CHAMPS internet-based telepathology platform facilitates the real-time viewing and discussion of whole slide images between the site and CPL pathologists during telepathology sessions for the purposes of consensus diagnoses, real-time bi-directional learning, and research. Prior to a telepathology session, when slides are available, both sites and CPL should scan, upload, and annotate all CHAMPS slides.

A. Standard Operating Procedures and Forms

The following provides a brief overview of the Telepathology and telepathology-related SOPs, forms and guidance documents (see [Master List of Standard Operating Procedures, Forms, and Other Documentation](#) for additional information).

Telepathology SOP (07.02.05)

The telepathology SOP describes the procedures for telepathology communications between the CPL, site Pathologists, other site Team Members and the CHAMPS PO, including case discussions, technical reviews, and training materials concerning CHAMPS cases. In addition to technical quality assessment, telepathology sessions facilitate real-time bi-directional learning and instruction for the identification of pathologic processes in tissues between the site and CPL pathologists. **Figure 14** provides the telepathology process flow.

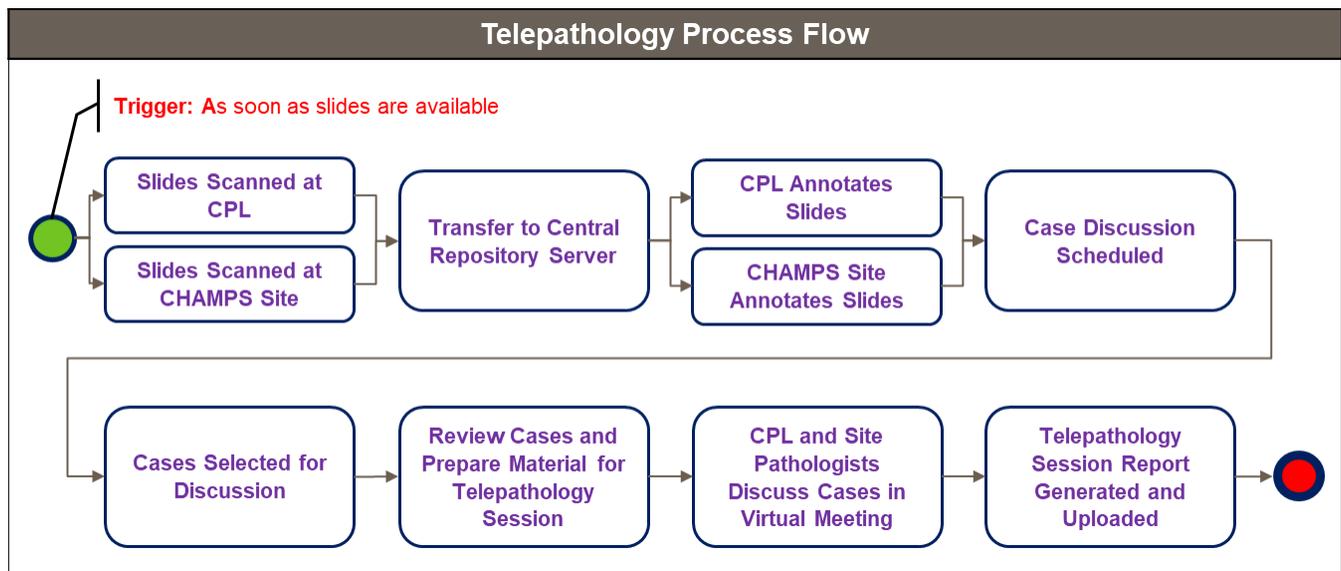


Figure 14: Telepathology process flow.

Annotation Using NanoZoomer Digital Pathology Viewer GD (07.02.05.01)

The annotation guidance document for annotating digitized slides provides steps for annotating digitized slides using the NanoZoomer Digital Pathology Viewer.

Telepathology Case Report Form (CRF 07.02.05)

The Telepathology Case Report Form captures site and CPL pathology findings, discussion points and final diagnosis for each CHAMP case discussed during the telepathology session.

Training Module (Biolucida for Medical Education) [In Development]

The CPL staff are in the process of developing a training module that will be hosted via Biolucida for Medical Education and credentialed through CDC's Secure Access Management System. Slides will be selected from

CHAMPS cases with frequently seen technical issues and pathologic processes and uploaded to the online training module for participating CHAMPS sites and the CHAMPS PO. The module will contain cases that are excellent examples of bacterial, viral, fungal, or protozoal infections, including H&E, SS, and IHC slides associated with the MITS cases. The module will also contain cases with common non-infectious processes. Slides will be annotated to highlight characteristic histopathologic patterns of disease and common technical issues. Selected slides will contain a de-identified, case overview (age, clinical syndrome).

Note: *A guidance document will be developed after the training module is fully developed. The document will explain how to access and use the online resource.*

6. Additional Future Testing

A. Pilots and Studies Under Consideration

Sickle Cell Disease Testing

Testing for sickle cell trait and sickle cell disease using DBS or whole blood, has been initiated in the CHAMPS diagnostic testing panel, starting with small pilot studies to identify a method adaptable across CHAMPS sites. Two sites (Mali and Kenya) started with using a commercial kit ([SickleScan™](#)) on retrospective cases. All sites will begin testing prospective cases starting in 2020. The DBS may also be used in the future to systematically conduct screening for other hemoglobinopathies and congenital diseases.

Antimicrobial Resistance

Antimicrobial resistance (AMR) testing is currently ongoing at most sites but testing methods and data collection have not been standardized across the CHAMPS Network. When AMR testing is standardized it will be added to the panel and included in this manual.

Serotyping or Further Characterization of Certain Pathogens

As significance of certain pathogens unfold in the CHAMPS Network, there may be a need for further characterization, such as serotyping for *Klebsiella pneumoniae*, *Escherichia coli*, and other pathogens.

B. Next-Generation Sequencing and Metagenomics

Next-generation sequencing (NGS) and metagenomics appear in principle to be more unbiased approaches to pathogen identification compared to algorithm-directed histopathology or PCR-based molecular diagnostics such as TAC. However, current metagenomics techniques have several limitations with respect to CHAMPS objectives for determining cause of death from patient specimens. Detection sensitivity through conventional PCR is typically on the order of 100 organisms, compared to 1,000-10,000 organisms from metagenomics. For NGS, sensitivity depends on the relative quantities of pathogen and host NA in the patient specimen, and consequently blood and tissue specimens are more complex to analyze compared to cell-free fluids such as CSF. The probability of pathogen detection is related to the number of sequencing reads (e.g., a novel astrovirus was discovered from brain tissue with 170 million sequencing reads of 100-300 nucleotides). Pathogens are occasionally missed during comparison with public sequence databases due to incomplete annotation and deposition into public sequence databases (e.g., [GenBank](#)). Research is currently being conducted at CDC to determine NA extraction methodologies that preserve the widest range of bacterial, fungal, and viral NA (both DNA and RNA). While NA extraction and short-read sequencing using [Illumina MiSeq System](#) or [Nanopore Technologies](#) are relatively straightforward, shotgun library construction and interpretation of sequence results requires sophisticated molecular biology and computational capacity which may be challenging to develop across the CHAMPS Network. Finally, the correlative rather than causative nature of diagnostic association, makes metagenomics primarily a supplementary technique at this time. However, the field of metagenomics is evolving rapidly. The following plans in descending priority and incorporation have been proposed to utilize current capacity of this powerful technology, to advance its validation for diagnostic purposes, and to develop valuable datasets.

Unexplained deaths with probable infectious etiology: Systematic metagenomics analyses may be conducted on cases for which histopathology has shown definitive evidence of inflammation, but no likely pathogen has been identified through IHC, PCR, TAC, or culture. These tissue specimens (to be determined according to pathology findings) will be subjected to NGS, followed by computational subtraction to remove the human DNA sequences. Pipelines such as [Sequence-based Ultra-Rapid Pathogen Identification](#) (SURPI) will be used to

search public databases for microbial sequences in a shortened timeframe. If microbial sequences are detected, the pathogen association will be attempted to be subsequently confirmed with conventional PCR or IHC (if available) on tissue or other specimens from the patient.

Host genetics: The consent form for CHAMPS MITS specimen collection include an option to allow for genetic testing to allow future research questions related to host genetics and the interaction between host and pathogens.

7. Non-Diagnostic Data Collection

Non-diagnostic data collection is the process of collecting data via VA and/or clinical abstraction. The sections below describe VA, the WHO 2016 VA questionnaires, and clinical abstraction (child and, if applicable, maternal).

A. Verbal Autopsy

When a stillbirth or death of a child U5 is identified in the CHAMPS area, the designated site personnel will electronically complete an Initial Death Notification Form. A designated site member will consult the Master Ledger on a daily basis to determine which cases need to be followed up for VA. The Master Ledger will indicate whether the family has given consent to be part of the CHAMPS project and if they have indicated that they will be available for follow-up. Families should be contacted to schedule the interview at a time and location that is convenient to them (within or as close as possible to the window period indicated on the Master Ledger). The designated site member will meet the family at the agreed upon time and place to conduct the VA interview.

All deaths under 5-years captured through CHAMPS mortality surveillance mechanisms will be approached to have a VA conducted. CHAMPS will use the 2016 WHO standard VA instrument (see following section below for a description of the WHO 2016 VA Questionnaires).

After the VA is conducted, a probable cause of death will be determined by physician review. Tissue sampling will be conducted for some reported deaths (if the cases were eligible for MITS and consent for the procedure was given). For these cases, the VA interview responses, together with other information about the death, will be provided to a panel of experts (DeCoDe Panel) to determine the ultimate cause of death of the individual child, neonate or stillbirth. If MITS consent was not granted and only VA consent and clinical abstraction consents were granted, the data will be evaluated via a Non-MITS DeCoDe Process.

WHO 2016 VA Questionnaires

The WHO 2016 VA questionnaires have been designed to collect information about the deceased from caregivers and family members. The information collected will be used by medical professionals to assign the probable cause of death. VA questionnaires include questions on the history of the final episode of illness, as well as symptoms and signs preceding death. There are three different questionnaires, each is specific to an age group:

- deaths of children aged under 4 weeks, for perinatal and neonatal deaths;
- deaths of children aged 4 weeks to 11 years, for post neonatal and child deaths; and
- deaths of adults aged 12 years and above, for adult deaths (**NOT USED FOR CHAMPS PURPOSES**).

The layout and question flow of all three questionnaires is guided by two basic principles. First, all three questionnaires follow the same general structure. Second, “skip patterns” (when an answer to a specific question results in bypassing or “skipping” other irrelevant questions) were employed to facilitate use by both medically and non-medically trained interviewers with differing levels of literacy.

The VA questionnaires are divided into several sections. Some of the sections are common to all three types of VA questionnaires and have the same general structure, while other sections are specific to certain questionnaires. The general structure of all three questionnaires includes specific content:

- information about the date and location of the verbal autopsy interview (i.e., age, sex, and place of death);

- specific information about the field site, household, and information related to residency in the assignment area;
- information about the primary respondent;
- socio-demographic information about the deceased;
- history of injuries/accidents;
- symptom duration checklist;
- health services used by the deceased during illness in the period before death, including whether a health worker informed the respondent of the cause of death;
- information that can be abstracted from a death certificate (if available);
- summary of any medical evidence available at the household; and
- short narrative history of events leading to death, and the cause of death according to the respondent.

The interview also includes an open narrative for the respondent to summarize in his/her own words the illness leading to the death. This information contributes to the process of diagnosing a most likely cause of death.

B. Clinical Abstraction

Clinical information pertaining to the deceased child as well and relevant maternal health information is abstracted for both MITS and non-MITS enrolled cases. Clinical records may be obtained from all levels of health facilities consulted during the child's terminal illness and/or death, antenatal care clinics, and in some cases may be obtained from family members.

Clinical information on the delivery and maternal health is abstracted for all stillbirths or deaths among infants aged <1 year. Records are also abstracted for deaths among children aged 1 year or older if the mother experienced complications or health problems during the pregnancy, labor, birth, or immediate postpartum period of the child in question [3].

Child Clinical Record Abstraction (SOP 06.02.04)

The purpose the Child Clinical Record Abstraction SOP is to standardize the processes and procedures of obtaining case medical records and completing the clinical abstraction case report forms. Detailed guidance is provided in the SOP for completing all the relevant forms (CRF 06.04.01 through 06.04.11) (**Note: These forms are currently in process of revision and the section will be updated when the forms are finalized**). The SOP describes procedures for abstraction of medical record data for all CHAMPS cases for which clinical records exist and are relevant to the child's health and course of illness. The child's health records are abstracted only after verifying that consent was given by the family to access the child's records (by parent or guardian), after completion of the Consent Authorization Form (06.09.01) and after verifying the child's identity.

The following are examples of the type of data abstracted from the child's various health records, when available:

- basic case information;
- physical examination records;
- past medical history;
- birth history;
- immunization records;
- growth charts;

- child and maternal HIV and TB information;
- diagnostic information; and
- clinical summary (transcribed from records or composed by abstractors based on available data).

Maternal Clinical Record Abstraction (SOP 03.02.00)

The Maternal Clinical Record Abstraction SOP provides guidance for standardization of procedures for accessing and abstracting maternal clinical records and instructions for completion of all the associated forms (CRF 03.02.01 through CRF 03.02.08) (**Note:** *These forms are currently in process of revision and the section will be updated when the forms are finalized*). Consent and completed consent authorization form is needed before accessing the mother's health information.

Examples of maternal health data abstracted from maternal clinical records when available (using the forms associated with this SOP), include:

- antenatal clinical history;
- pregnancy labor and delivery;
- placenta and cord description;
- maternal laboratory testing and treatments;
- maternal medications;
- maternal transfusions, information on previous pregnancies and pregnancy outcomes;
- perinatal outcome and basic characteristics of the enrolled deceased child; and,
- if applicable, maternal death information.

Maternal Registry (SOP 03.01.00 or 11)

The purpose the Maternal Registry SOP is to standardize the processes and procedures for obtaining basic maternal demographic and pregnancy information.

The SOP describes procedures for collecting and documenting basic maternal demographic and pregnancy history data into the CHAMPS Maternal Registry. This applies only to biological mothers of CHAMPS-enrolled stillbirth or child cases, or women enrolled in CHAMPS pregnancy surveillance. The Maternal Registry Forms (CRF 03.01.00 Series) collect maternal demographic information (CRF 03.01.01), historical or current pregnancy and pregnancy outcome data for all pregnancies (CRF 03.02.02 and CRF 03.02.03), and maternal death information, if applicable (CRF 03.01.04).

A completed consent authorization form is required to collect the data for the Maternal Registry.

III. Determination of Cause of Death (DeCoDe)

The DeCoDe is determined by a panel consisting of clinical, microbiology, pathology and public health experts that review, discuss, and come to consensus on the cause(s) of the death based on all available data consented to and shared by the family.

1. MITS DeCoDe Process

A process for determination of cause of death for stillbirths and child death (U5 years of age) across the CHAMPS Network has been developed using panels of experts from each site. The site panels use the information provided to ascertain the underlying cause (event that precipitated the fatal sequence of events) and other antecedent, immediate, and maternal causes of death in accordance with the ICD-10 and the WHO Medical Certificate of Cause of Death. CHAMPS DS have been developed (see [Supplemental Materials](#)) to provide a framework of required evidence to support cause of death determination and to ensure uniform procedures for a more consistent interpretation of complex data across the CHAMPS Network. The standardized DeCoDe process for CHAMPS will also enable in the future comparability with other sources of mortality data produced by initiatives external to CHAMPS. Early lessons learned from implementation of DeCoDe in five CHAMPS sites have been incorporated into the current DeCoDe process [9]. The procedures established for CHAMPS sites to determine cause of death include:

- a standardized system for data collection, management, QC and review;
- standardized processes for cause of death determination;
- analysis of all relevant information by a multidisciplinary panel composed of local experts from each CHAMPS site including: laboratory, histopathology, abstracted clinical records, and VA findings and, if applicable clinical information for the mother;
- use of internationally accepted standards for classification and coding of cases adapted for CHAMPS;
- training of site coordinators and panel members, to ensure that uniform processes and standards for cause of death determination will be applied across CHAMPS Network sites; and
- a QA process to examine how CHAMPS DS are applied across sites, by selecting a set of cases for review by cross-site panels and external SMEs. Incorporating lessons learned to ensure consistent application of CHAMPS data and improve the accuracy of cause of death determination across sites.

Additional information about the DeCoDe process and data quality monitoring are included in the Introduction to this manual (see [Overview of CHAMPS](#)

Introduction to CHAMPS).

A. Standard Operating Procedures and Forms

The following sections provide an overview of DeCoDe SOPs, forms, and documentation (see [Master List of Standard Operating Procedures, Forms, and Other Documentation](#)).

Determination of Cause of Death (DeCoDe) Process SOP (08.00.01)

The purpose of the SOP is to describe the procedures for recruitment and training of DeCoDe panel members, for case review and cause of death determination processes and for recording results of the DeCoDe proceedings. The SOP details:

- composition and responsibilities of all personnel involved in the DeCoDe process;

- required training for panel members depending on their responsibilities;
- the role and responsibilities of the case manager including but not limited to: coordinating the panel, reviewing all case data, assembling DeCoDe Case Packets, disseminating the data packages to the panelist, moderating the panel discussions (if Case Manager is also Panel Chair) and submitting DeCoDe packet to WebPortal;
- DeCoDe process;
- assigning cause of death and assigning level score;
- panel review process;
- ICD-10 coding of the panel report by a trained site member and final data quality checks; and
- DeCoDe results submission process.

Included in the appendix to SOP 08.00.01 are the following materials and forms:

- Case Packet Summary (**SOP Appendix A**); the case packet is assembled by the case manager and sent to all members of the DeCoDe panel.
- Definitions of Consensus Categories (**SOP Appendix B**)
- DeCoDe Panel Form, CRF 08.00.02 with instructions (**SOP Appendix C**)
- DeCoDe Panel ICD-10 Form, CRF 08.00.06 with instructions (**SOP Appendix D**)

Included in the Related Documents section of SOP 08.00.01:

- Determination of Cause of Death (DeCoDe) Diagnosis Standards: Guidance for Standardized Interpretation of CHAMPS Data (CHAMPS Diagnosis Standards) (**SOP Section 4: Related Documents**)
- ICD-PM (**SOP Section 4: Related Documents**)

DeCoDe Panel Form (CRF 08.00.02)

The DeCoDe Panel Form is completed during the panel meeting to record the order of the cause(s) of death that are agreed upon by a majority of the panelists. Additional information collected in CRF 08.00.02: the overall data elements most influential in the determination of the immediate and underlying causes of death, any information not represented in the DeCoDe Case Packet that was reviewed by the panel and essential to cause of death determination, any comments on the case and the panel's recommendations for public health action.

DeCoDe Panel ICD-10 Form (CRF 08.00.06)

The DeCoDe Panel ICD-10 Form is prepopulated with information from CRF 08.00.02. The responsible ICD-10 Coder completes the prepopulated CRF 08.00.06 with ICD-10 codes.

CHAMPS Diagnosis Standards

CHAMPS DS have been developed to provide a framework of required evidence to support cause of death determination and to ensure uniform procedures for a more consistent interpretation of complex data across the CHAMPS Network. Standardization of DeCoDe for CHAMPS will enable future comparability with other sources of mortality data produced by initiatives external to CHAMPS.

ICD-10

ICD-10 is the 10th revision of the International Statistical Classification of Diseases and Related Health Problems, a medical classification list by the WHO. It contains codes for diseases, signs and symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or diseases.

ICD-PM (Perinatal Mortality)

ICD-PM, like ICD-MM (Maternal Mortality), is based on the 10th revision of the ICD-10 and its coding rules. It is intended to facilitate the consistent collection, analysis and interpretation of information on perinatal deaths (16).

Advanced Photography Analysis SOP (06.02.03)

This SOP describes procedures for analyzing and documenting photographs of the body obtained during the MITS procedure (for cases consented to MITS and photography), for the primary purpose of assessing any visible birth defects or congenital malformations. The SOP includes procedures for assessing and documenting injuries that may indicate physical (or sexual) violence against the child. Refer to the MITS Procedure (SOP 06.02.01) and MITS Specimen Collection Form (CRF 06.02.01) for more information.

2. Non-MITS DeCoDe Process

Cause of death determination for non-MITS cases is based on information obtained from clinical abstraction and VA.

The non-MITS DeCoDe process is applied to cases that meet CHAMPS requirements for enrollment based on catchment area and age of deceased child, but are either not eligible for MITS (body of deceased child is not available, or the allowable interval from time of death has been exceeded), or the family does not consent to the MITS procedure (see **CHAMPS Mortality Surveillance Process** Figure 3).

A similar process to MITS DeCoDe, using expert review of information is envisioned by the CHAMPS PO and remains to be established. The CHAMPS PO is also considering issuing guidance for non-MITS data analysis and strategies for use of data from non-MITS cases.

Note: *This section will be updated when the DeCoDe process for non-MITS cases is finalized.*

3. Notifiable Conditions

For CHAMPS MITS cases in which laboratory or other CHAMPS data suggest the presence of a notifiable condition, TB, HIV, or other conditions that might require public health action, the CHAMPS PO is developing standardized procedures for identifying cases, following-up with families and public health authorities, and documenting public health actions.

For notifiable conditions, it may be necessary to contact the family prior to the DeCoDe panel cause of death determination to discuss medical findings. To address circumstances that require contacting the family prior to DeCoDe results, a separate process (currently being developed) will outline the steps site staff should take when contacting and meeting with the family.

Note: *The Notifiable Conditions Process has not been finalized at this time. This section will be updated once the process is finalized.*

4. Family Follow-up

All sites are required to deliver the DeCoDe panel cause of death determination results to the family within a reasonable timeframe. The process of delivering the results to the family starts with the site personnel such as a case manager reviewing the cause of death determination with other site personnel such as the CHAMPS community liaison and clinician. The case manager discusses any specific considerations (religious considerations, circumstances around the death, etc), ensures the community liaison and clinician understand the information to be delivered and can answer questions from the family. Following the case briefing, the community liaison/clinician arrange a date and time with the family to meet. The community liaison/clinician meet with family, discuss the results, refer the family to applicable services and resources, and ask if there are any questions. Immediately following the family visit, the community liaison/clinician complete the appropriate form to document the visit.

Note: *In cases where public health action is recommended, the case manager provides the community liaison/clinician with informational resources to provide to the family. Additionally, case manager and site safety monitor will need to coordinate with local public health authorities to ensure there is appropriate follow-up.*

A. Standard Operation Procedure and Forms

The following sections provide an overview of the Family Follow-Up SOP and DeCoDe Panel Feedback form (see [Master List of Standard Operating Procedures, Forms, and Other Documentation](#)).

Family Follow-Up SOP (06.03.01)

The purpose the Family Follow-Up SOP is to standardize the process and procedure for delivering final cause of death information to families who consented to the MITS procedure, including how to complete appropriate forms and brief staff members on relevant case information. The SOP appendix contains instructions for accurately completing the DeCoDe Panel Feedback Form (CRF 06.03.02).

DeCoDe Panel Feedback Form (CRF 06.03.02)

The DeCoDe Panel Feedback Form documents the family follow-up visit, the DeCoDe results provided to the family; if applicable, any public health action recommendations/suggested consultations, family feedback, comments or questions, attendees present, and any comments/observations noted by the CHAMPS staff.

IV. References

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1. Data Quality Specifications [Placeholder]

2. Related Documents [Placeholder]

V. Appendix

1. Master List of Standard Operating Procedures, Forms, and Other Documentation

A. Standard Operating Procedures

Name of Standard Operating Procedure	Document Control Number
Death Notification and Eligibility Screening	SOP 06.01.01
Consent Process	SOP 06.01.02
Transport of Body	SOP 06.01.03
MITS Procedure	SOP 06.02.01
Specimen Accessioning and Distribution	SOP 07.00.01
Biorepository	SOP 07.04.02
International Shipment of Specimens	SOP 07.04.03
Tissue Processing	SOP 07.02.01
Tissue Sectioning	SOP 07.02.02
H&E Staining	SOP 07.02.03
Special Stains	SOP 07.02.04
IHC Testing	SOP 07.02.0X
TaqMan Array Card Testing	SOP 07.01.01
Supplemental TAC Analysis	SOP 07.01.01.01
TAC Assay Appendix	SOP 07.01.01.02
Blood and CSF Extraction	SOP 07.01.02.01
Respiratory Swab Extraction	SOP 07.01.02.02
Rectal Swab and Stool Extraction	SOP 07.01.02.03
Tissue Extraction	SOP 07.01.02.04
Telepathology	SOP 07.02.05
Child Clinical Record Abstraction	SOP 06.02.04
Maternal Clinical Record Abstraction	SOP 03.02.00

Maternal Registry	SOP 03.01.00 or 11
DeCoDe Process	SOP 08.00.01
Advanced Photography Analysis	SOP 06.02.03
Family Follow-Up	SOP 06.03.01

B. Forms

Name of Form	Document Control Number
Disposition of Body Form	CRF 06.01.04
MITS Specimen Collection	CRF 06.02.01
Placenta Gross Examination	CRF 07.00.13
Clinical Laboratory Results	CRF 07.00.03
Blood Microbiology Results	CRF 07.00.04
Lung Microbiology Results	CRF 07.00.12
TAC Tracker	CRF 07.01.01
Gross Examination	CRF 07.00.09
Placenta Microscopic Examination	CRF 07.00.14
Site Pathology Report	CRF 07.00.05
CPL Results (IDPB Pathology Report)	PDF Form, not in RedCap
Telepathology Report Form	CRF 07.02.05 (Not a formal REDCap form)
Child Clinical Record Abstraction	CRF 06.04.01 - 06.04.11
Maternal Clinical Record Abstraction	CRF 03.02.01 - 03.02.08

Maternal Registry	CRF 03.01.00 Series
DeCoDe Panel ICD-10	CRF 08.00.06
DeCoDe Panel	CRF 08.00.02
DeCoDe Panel Feedback	CRF 06.03.02

C. Guidance Documents

Name of Guidance Document or User Guide	Document Control Number
Biosafety Guidance for MITS Specimen Collection	UG 06.02.07
Guidelines for Infection Prevention and Control	UG 06.01.04
Guidance for Transferring the Tissue Specimens	GD 06.02.01.01
TAC <i>Streptococcus pneumoniae</i> Serotyping (Spn TAC_CDCv1)	TBD
Annotation Using NanoZoomer Digital Pathology Viewer	GD 07.02.05.01
WHO 2016 VA Questionnaires	CD 04.00.01 (ODK V2.04)

D. Supplemental Materials

Name of Supplemental Material	Document Control Number
CHAMPS Diagnosis Standard	N/A
ICD-PM (The WHO Application of ICD-10 to Deaths During the Perinatal Period: ICD-PM)	N/A
ICD-10 (10th revision of the International Statistical Classification of Diseases and Related Health Problems)	N/A

E. Other Documentation

Name of Document	Document Control Number
Diagnostic Plan Change Management	

