ToolCAP: Novel Tools to improve management of paediatric Community-Acquired Pneumonia - a randomized controlled trial

Study Type:	Other Clinical Trial according to ClinO, Chapter 4 *(Template used: V1.3, 20.07.2022 used)*
Risk Categorisation:	Risk category A according to ClinO, Art. 61
Study Registration:	Registration Sites: 1. Clinicaltrials.gov: - NCT 06670833 2. Pan-African Clinical Trails Registry: - PACTR20241282257G3G7 3. South African National Clinical Trials Register: - DOH-27-052025-7467
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Investigated Intervention:	IMCI-PLUS clinical management algorithm for antibiotic prescription in paediatric pneumonia
Protocol ID	Pending
Protocol Version and Date:	Version 3.0_Wits (dated 07/11/2025)

CONFIDENTIALITY STATEMENT

The information contained in this document is confidential and the property of the Sponsor-Representative Overall Coordinating Investigator. The information may not - in full or in part - be transmitted, reproduced, published, or disclosed to others than the applicable Competent Ethics Committee(s) and Regulatory Authority(ies) without prior written authorisation from the Sponsor except to the extent necessary to obtain informed consent from those who will participate in the study.

CHANGE HISTORY TABLE

Version	Affected Section(s)	Summary of Revisions	Rationale
v.2.0 17.06.2024	N/A	First submitted and approved version	N/A
v.3.0 20.10.2025	All changes below refer to sections, pages and text in the main protocol. The protocol synopsis has been amended in line with the changes to the main protocol. Page numbers in this table refer to those in the tracked version of the protocol.		
	Entire Document	Minor grammatical, editorial and formatting corrections throughout.	To improve clarity and readability; no change to study content or intent.
	Title page	Removed the Informed Consent versions from the protocol	To avoid needing the protocol amended should an informed consent document require updating. Informed consent documents and version trackers are available in the Investigator Site Files.
	2. Study Administrative Structure: Sponsor Representative, Overall Coordinating Investigator *(Title page and page 27)*	Sponsor updated from University of Bern (UBern) to EPFL following investigator's institutional move.	To reflect current sponsor and investigator affiliation.
	2. Study Administrative Structure: Site PI in Tanzania *(Title page and page 27)*	Adjustment of Prof Nahya Salim from investigator to Principal Investigator at the MUHAS site in Tanzania	To appropriately reflect the study team at the MUHAS site
	2. Study Administrative Structure: Site Investigators *(Pages 27, 28)*	Removed individual investigator names; section now refers to site-specific delegation logs and related documents.	To allow flexibility for investigator additions or removals without requiring protocol amendments; no changes to investigators since original submission.
	4.1 Hypothesis and Primary Objectives Primary Objectives *(Page 32)*	Clarified age criteria to specify inclusion of children aged ≥60 days and <13 years. No change to age cut-offs for inclusion in the study.	To improve standardised interpretation of upper age threshold (i.e., includes the 60th day and the entire 12th year of life).

	4.1 Hypothesis and Primary Objectives Secondary Objectives *(Page 33)*	Secondary Objective 2.2 “To compare, where available, the aetiological diagnosis between the intervention and control group” moved to Exploratory Objective.	Biological samples for aetiology testing are not collected from all participants (subject to specific caregiver consent and feasibility of collection, storage and transport per site), therefore this objective was moved from secondary to exploratory.
	4.1 Hypothesis and Primary Objectives Secondary Objectives *(Page 33)*	Secondary Objective 2.2 for the TB substudy restructured and reworded.	To improve the understandability and clarity of the objectives related to the TB substudy, and remove some duplication. No change to the content of the objectives.
	4.2 Primary and Secondary Endpoints *(Pages 34, 35)*	This section was re-formatted so that each objective was correctly mapped to its corresponding endpoint.	To make it clearer that each objective has a linked measurable endpoint.
	4.3 Study Intervention 4.3.1.1 Lung ultrasound *(Page 36)*	Age expressed as ‘>6 months to <5 years’ in place of ‘2-59 months’ and ‘<13 years’ instead of ’12 years’.	To improve ease of interpretation
	4.3 Study Intervention Table 1 *(Page 38,39)*	Table re-sketched for improved readability; references to specific “anticipated” antibiotics removed. Footnote simplified to remove detailed country-specific treatment guideline context.	To enhance clarity and avoid confusion, as antibiotic selection is not part of the intervention. Formatting improved for readability without altering content.
	4.3.1 - 4.3.2 – Non-Admitted Patients & Control Group Management *(Page 39)*	Minor wording clarifications: replaced “guidelines” with “framework”; specified “approximately” Day 3; added “for children with IMCI-pneumonia” and “by the research team”; clarified guideline applicability for children <5 years vs ≥5 years	To improve precision and consistency in describing follow-up timing, age applicability, and responsibility for assessments; no change to study intent or procedures.
	Figure 2: Flow Diagram of Study Procedures *(Page 40,41)*	Clarified that TB substudy enrolment may occur at any time between D1–D8 (not only at D8). Updated telephone follow-up procedures to specify home visits for participants who remain uncontactable.	To accurately reflect study procedures and improve clarity on participant follow-up processes; no change to study design or intent.
	4.4 Study Design:	Revised section to clarify that clinicians are expected to	To ensure appropriate clinician

	Methods of Minimising Bias *(Pages 42,43)*	exercise clinical discretion and overrule LUS-based antibiotic recommendations when clinically appropriate; such decisions are not considered protocol deviations but reasons will be recorded. Section retitled “Clinical Discretion and Potential Impact on Study Outcomes.”	autonomy while accurately describing factors that may influence study outcomes.
	5.1 Inclusion and exclusion criteria, justification of study population: Inclusion Criteria *(Page 44)*	Clarified age criteria to specify inclusion of children aged ≥60 days and <13 years. No change to age cut-offs for inclusion in the study.	To improve standardised interpretation of upper age threshold (i.e., includes the 60th day and the entire 12th year of life).
	5.1 Inclusion and exclusion criteria Exclusion Criteria *(Page 44)*	Revised wording from “Received antibiotic treatment for more than 48 hours at the time of enrolment” to “Currently taking antibiotic treatment for more than 48 hours at the time of enrolment.”	To improve clarity and ensure consistent interpretation of ongoing antibiotic use at the time of enrolment.
	5.2 Recruitment, Screening and Informed Consent *(Page 46)*	Added clarification that study staff will screen all potentially eligible participants presenting during study operating hours.	To ensure transparency regarding screening procedures and to address any potential concerns about selection bias related to staff availability.
	5.3.1 Data Collection Clinical Baseline Data *(Page 47)*	Added that information about birth history and history of receiving routine deworming and Vit A prophylaxis will be collected at the time of study enrolment from participant clinic cards.	To ensure possible risk factors (eg prematurity) that could be linked to outcomes are captured and documented.
	5.3.1 Data Collection Secondary Outcomes *(Page 48)*	Additional text added / text amended to clarify that children with clinical failure at D8 or persistent/recurrent symptoms at D29 will be enrolled into the TB substudy, followed up and appropriately linked to care.	To ensure consistency in the protocol around the D8 and D29 visit outcomes, linked to the TB substudy.
	5.3.2 Follow-up of Participants: *(Page 49)*	Rephrased heading and text to clarify that follow-up visits requested by the treating clinician are considered “unscheduled study visits” rather than “spontaneous/unplanned” visits.	To improve clarity and distinguish between scheduled study visits and clinician-initiated routine follow-ups, ensuring consistent classification of visit types.

	5.3.3 Exploratory Outcomes and additional Investigations LUS Performed in Control Group (*Pages 49, 50)*	(1) Clarified that LUS will be collected at all in-person participant engagements where feasible, not limited to Day 1. (2) Added guidance that in some circumstances, certain abnormal LUS findings in the control group (e.g., empyema, pneumothorax, suspected mass) may be disclosed following discussion with the site coordinator and documentation on a protocol deviation form; interpretation remains at the discretion of the study clinician within the limits of their training.	To accurately reflect intended study procedures and provide ethical guidance for handling clinically significant incidental findings while maintaining study integrity.
	Lung Auscultation *(Page 50)*	Updated lung auscultation acquisition protocol to reflect fewer regions recorded; corresponding figure revised for consistency.	To align the protocol and figure with the finalised lung sound recording procedure while maintaining methodological clarity.
	5.3.4 Sample Collection and Biobanking *(Pages 50,51)*	(1) Removed reference to DBS samples and reduced intended blood volumes to align with updated assay requirements and ethical collection limits. (2) Clarified distinction between samples collected for current study assays and those retained for "future use" under separate consent and biobanking procedures.	To ensure ethical sample volume collection and clearly differentiate between samples analysed within the study and residual specimens stored for future approved research.
	5.3.4 Sample Collection and Biobanking Table 2 *(Pages 51,52)*	Updated to more accurately reflect the order and timing of study procedures, incorporating clarifications made in related sections (e.g., LUS collection, follow-up procedures, and sample collection).	To ensure internal consistency and accurately represent the sequence and timing of study activities.
	5.5 Inclusion into Observational Cohort Study *(Page 52)*	Added minor clarifications regarding intended LUS collection time points and phone/in-person follow-up procedures to improve clarity.	To ensure clear description of procedures without altering original study intentions or design.
	5.6 Inclusion in the TB Substudy *(Pages 52,53)*	TB substudy eligibility essentially the same but text added and amended for clarity. Only additional criteria for enrolment in the TB substudy that has been added is 'TB exposure during the study period'.	To improve ease of interpretation of the TB substudy eligibility (eg 'meeting all inclusion criteria but also any exclusion criteria 1-9' of the RCT refers to the Observational cohort population and is now expressed more clearly.

		Added text to clarify that enrolment into the TB substudy may have some variation by site depending on capacity and feasibility which would outlined in the Study Manual of Operation for each site	To ensure that children with TB exposure over the study period, who are at higher risk of having TB disease, are enrolled, investigated and appropriately linked to care. To allow for some flexibility in TB substudy enrolment/implementation between sites, depending on feasibility and capacity.
	5.6 Inclusion in the TB Substudy *(Page 53)*	Clarification of venous blood sample volume for TB biomarker testing, and inclusion of a statement about adherence to international norms for safe blood volume limits for paediatric research. Addition of text to allow for the Week 8 TB substudy visit to be done in-person, if feasible.	To clarify blood volume requirements and provide assurance that study blood volumes will never exceed the recommended limits. To allow flexibility to perform the Week 8 TB substudy visit in person, allowing for more reliable clinical evaluation.
	6. Statistics and Methodology 6.1 Statistical analysis plan and sample size calculation *(Pages 53,54)*	Removed the assumption that participants missing D8 follow-up would be classified as not experiencing clinical failure for ITT analysis; clarified that the primary outcome will be assessed for superiority using both ITT and per-protocol sets; added detail on handling rare outcomes (e.g., death) with non-parametric or small-sample tests and specified use of the Wilcoxon rank-sum test for hospitalization duration; removed reference to linear regression for continuous secondary outcomes; expanded final sentence to note inclusion of estimands framework in the SAP	To align analysis descriptions with current statistical approach, ensuring clarity on handling of missing data, outcome testing methods, and consistency with the planned Statistical Analysis Plan.
	6. Statistics and Methodology 6.2 Handling of missing data and drop-outs	Replaced previous description of handling missing follow-up data with a multiple imputation approach under a missing-at-random assumption; removed prior wording that classified participants with missing D8 follow-up as not experiencing clinical failure; retained	To align with updated statistical methodology for handling missing data and ensure clarity on analytic assumptions.

	(Pages 54)	reference to SAP for full methodological details.	
	7. Regulatory aspects and Safety 7.2 Adverse Events *(Page 57)*	Added reference to Senegal	To ensure clarity on adverse event reporting across all sites
	7.3 (Periodic) safety reporting *(Page 58)*	Clarified that the Annual Safety Report (ASR) is submitted at least once per year, and that more frequent reporting may occur if required by local regulations.	To improve clarity and accuracy of safety reporting procedures, ensuring alignment with regulatory requirements and allowing flexibility for locally mandated reporting frequency.
	7.6 Insurance *(Page 58)*	Noted that insurance would not be purchased by the sponsor, but rather the institution conducting the study	For clarity
	9.3 Confidentiality and coding 9.3.1 Data management and Coding *(Page 60)*	Clarified data-handling procedures: replaced statement that participants are only identified by ID numbers with wording indicating that identifying data will be available only to authorised site research staff; added note that all participant files will be securely stored; removed redundant phrasing about access restrictions.	To strengthen clarity on confidentiality, specify controlled access for authorised staff, and align with best practices for secure data storage and protection.
	9.3.5 Retention and destruction of study data and biological material *(Page 61)*	Added details regarding Stellenbosch biobank facilities to match details in Section 5.3.4	For consistency

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GLOSSARY OF ABBREVIATIONS

AE	*Adverse Event*
AI	*Artificial Intelligence*
AMR	*Antimicrobial Resistance*
ASR	*Annual Safety Repot*
AUC	*Area Under the Curve*
AUROC	*Area Under the Receiver Operator Curve*
BASEC	*Business Administration System for Ethical Committees*
CI	*Confidence Intervals*
ClinO	*Ordinance on Clinical Trials in Human Research (in German: KlinV, in French: OClin, in Italian: OSRUm)*
CE	*Conformité Européenne*
COVID	*Coronavirus disease*
CPAP	*Continuous Positive Airway Pressure*
CRF	*Case Report Form*
CRP	*C-Reactive Protein*
CT	*Computed Tomography*
CTCAE	*Common Terminology Criteria for Adverse Events*
CXR	*Chest X-Ray*
EPFL	*École Polytechnique Fédérale de Lausanne*
FADP	*Federal Act on Data Protection (in German: DSG, in French: LPD, in Italian: LPD)*
eCRF	*electronic Case Report Form*
EDC	*Electronic Data Capture*
ER	*Emergency Room*
FOPH	*Federal Office of Public Health*
GCP	*Good Clinical Practice*
GDPR	*General Data Protection Regulation*
HIV	*Human Immunodeficiency Virus*
HRA	*Human Research Act (in German: HFG, in French: LRH, in Italian: LRUm)*
ICH	*International Conference on Harmonisation*
IDMC	*Independent Data Monitoring Committee*
IM	*Intramuscular*
IMCI	*Integrated Management of Childhood Illness*
IMCI-PLUS	*IMCI-Point-of-care Lung Ultrasound*
ISBER	*International Society for Biological and Environmental Repositories*
ITT	*Intention to Treat*
LUS	*Lung Ultrasound*
LAusc	*Lung Auscultation*
LRTI	*Lower respiratory tract infection*
LTFU	*Lost to Follow-Up*
MRI	*Magnetic Resonance Imaging*
MUHAS	*Muhimbili University of Health and Allied Sciences*
NICD	*National Institute for Communicable Diseases*
NPV	*Negative Predictive Value*

OPD	*Outpatient Department*
PCT	*Procalcitonin*
POPIA	*Protection of Personal Information Act*
PPV	*Positive Predictive Value*
PTB	*Pulmonary Tuberculosis*
RCT	*Randomised Controlled Trial*
RSV	*Respiratory Syncytial Virus*
SAE	*Serious Adverse Event*
SAM	*Severe Acute Malnutrition*
SDLL	*Source Data Location List*
SSA	*Sub-Saharan Africa*
STAT	*Immediately*
Swiss TPH	*Swiss Tropical Public Health Institute*
TAP	*Technical Advisory Panel*
TB	*Tuberculosis*
UTM	*Universal Transport Medium*
WHO	*World Health Organisation*

1 STUDY SYNOPSIS

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Study Title	**ToolCAP**: Novel **Tool**s to improve management of paediatric **C**ommunity-**A**cquired **P**neumonia – a randomized controlled trial
Short Title / Study ID	ToolCAP
Protocol Version & Date	Version 3.0 (dated 20/10/2025)
Study Registration	Registration Sites: 1. Clinicaltrials.gov: NCT 06670833 2. Pan-African Clinical Trails Registry: PACTR20241282257G3G7 3. South African National Clinical Trials Register: DOH-27-052025-7467
Study Category and Rationale	Other clinical trials (ClinO chap. 4), Category A: The intervention under evaluation is a decision support tool which has only limited risks. This study will not involve the use of unregistered medicinal products or medical devices
Background and Rationale	In 2019, lower respiratory tract infections (LRTI) caused 2.6 million deaths worldwide, making them the fourth leading cause of death overall. While the statistic is global the effect is concentrated in low-resource settings and among children, with pneumonia being the single largest infectious cause of death in children worldwide. LRTI (including pneumonia) are the most common reason for sick children to present for acute outpatient care and current best practice pneumonia management guidelines advocate for all cases to receive a course of antibiotics, based on the World Health Organization's (WHO) Integrated Management of Childhood Infections (IMCI) guidelines, first developed in the 1990s - a time when providing access to antibiotics was a major goal for public health programs. These guidelines rely on presumptive antibiotic treatment based on clinical signs alone (cough, respiratory rate, and lower costal indrawing) despite these clinical features inadequately distinguishing bacterial causes of pneumonia from the vastly more common, self-limiting viral infections. Recent evidence currently estimates that bacterial causes of respiratory infections in sub-Saharan Africa (SSA) make up as low as 2-4% of LRTI cases in the primary care setting, and 23.3-31.6% in the secondary/hospital setting. Considering that bacterial antimicrobial resistance (AMR), responsible for 1.27 million deaths in 2019, has become a public health crisis in SSA, effective tools to safely identify the minority of children requiring antibiotics are essential. This would enable frontline clinicians in low resource settings to move away from prescribing antibiotics to nearly every child; a practice currently driving antibiotic overuse and fuelling local antimicrobial resistance whilst significantly overtreating cases of viral pneumonia. Improving IMCI diagnostic criteria to better identify children with pneumonia that would benefit from antibiotic therapy is therefore a WHO research priority, along with a growing interest in the potential of Lung Ultrasound (LUS) to address this. LUS has now become increasingly affordable in low-resource-settings thanks to recent innovations in its "ultrasound-on-a-chip" design; now pluggable into a mobile device it could be integrated into the standard clinical exam without incurring extra costs, time, radiation, or specialist consultation. This, together with increasing evidence showing its ability to effectively detect lung consolidation in pneumonia, have made it an attractive tool for frontline clinicians. Most studies, performed in high-income tertiary care settings, have found the diagnostic performance of LUS comparable with that of CXR (meta-analysis: overall sensitivity 95 %, 91–97 %; overall specificity 96 %, 90–99 %). Studies in low- to middle-income countries (LMIC) are equally promising, as seen in Nepal, Peru, and Egypt, yet remain limited in scope and context, with no evidence on the clinical impact of LUS assisted diagnoses on antimicrobial use or health outcomes, particularly in a primary care setting. Although some studies have assessed the ability of LUS to differentiate viral from bacterial infections, their findings have been limited with the largest challenge being reliable reference standards for bacterial pneumonia. The difficult of generating accurate reference standards is most notably explored in the large Pneumonia Etiology Research for Child Health (PERCH) study which shows how children tend to have a vast number of bacteria and viruses present in

<table>
<tr><td></td><td colspan="2">their respiratory tract at any given time, making it hard to definitively prove which is the primary cause of an illness without using extensive and expensive tests. This is however a common challenge as seen in similar studies assessing the ability of CXR to do the same. This lack of a microbiologically confirmed diagnosis makes it hard to make definitive statements about the ability of LUS to differentiate. This highlights the importance of the assessment of LUS integrated into care to assess for real changes in treatment outcomes through an interventional study, rather than observational diagnostic accuracy studies.

We therefore propose that the integration of lung ultrasound (LUS) (including standardised interpretation) into the IMCI-based management guidelines of clinical pneumonia will better identify those who would benefit from antibiotic treatment, which will lead to a reduction in antibiotic overuse without compromising health outcomes.</td></tr>
<tr><td>Objectives & endpoints</td><td colspan="2">
<table>
<tr><th>Primary objectives</th><th>Primary endpoints</th></tr>
<tr><td>1.1 To evaluate whether the integration of LUS into current IMCI-based management guidelines for pneumonia (intervention group) reduces antibiotic treatment at D1 among children aged ≥60 days - <13 years with WHO IMCI clinical pneumonia, when compared to routine care (control group).</td><td>1.1 Proportion of participants prescribed antibiotic treatment on D1.</td></tr>
<tr><td>1.2 To evaluate whether the integration of LUS into current IMCI-based management guidelines for pneumonia (intervention group) is non-inferior in terms of clinical failure by D8 among children aged ≥60 days - <13 years with WHO IMCI clinical pneumonia, when compared to routine care (control group).</td><td>1.2 Proportion of participants with clinical failure, defined as the development of any of the following criteria during the specified time periods after enrolment.
i. Any time before or on D8:
• WHO IMCI danger sign (inability to drink/breastfeed, vomiting everything, convulsions with this illness, lethargy/unconscious)
• New or worsening severe respiratory distress (such as grunting, head nodding, severe chest indrawing)
• Secondary Hospitalization (defined as a hospitalization occurring after discharge from in-patient admission or outpatient visit) related to a deterioration of the presenting complaint on D1
• Change in level of care (e.g., admission to intensive care unit, transfer to higher level of care)
• Need for respiratory support (e.g., high flow nasal cannula, CPAP)
• Death due to any medical cause (i.e., except trauma)
ii. At D8 outcome assessment:
• Report from the caregiver of non-resolution/worsening of illness</td></tr>
<tr><th>Secondary objectives</th><th>Secondary endpoints</th></tr>
<tr><td>2.1 To assess the effect of the intervention (when compared to routine care) in children with WHO IMCI clinical pneumonia on:

i. the proportion of children prescribed antibiotics by D8
ii. the proportion of adverse drug reactions related to routine antibiotic treatment by D8 (i.e., Anaphylactic reaction, severe diarrhoea, or generalised severe rash).</td><td>2.1 Evaluation of the effect of the intervention in children with clinical pneumonia on:

i. The proportion of children prescribed an antibiotic by D8.
ii. The proportion of adverse drug reactions related to routine antibiotic treatment by D8 (i.e., Anaphylactic reaction, severe diarrhoea, or generalised severe rash).</td></tr>
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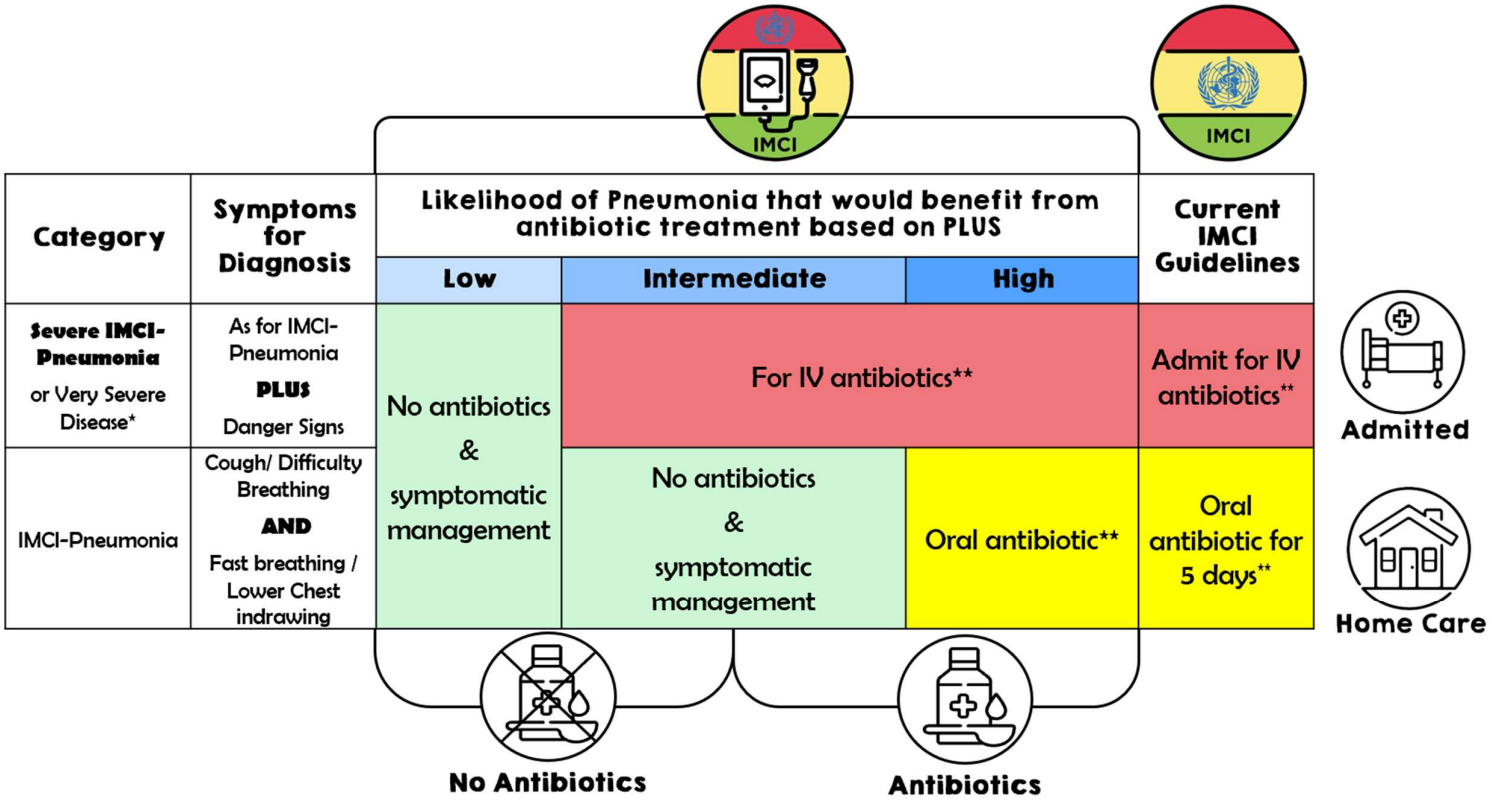
	iii. the proportion of participants cured (defined as caregiver-reported recovery from illness) by D8 and D29 (for those not cured at D8) iv. the proportion and duration of inpatient admissions by D8 and D29 (for those admitted on D1 only). v. the use of diagnostic tests (in addition to LUS) on D1, and for those admitted, by D8. vi. death by D29 **vii.** the proportion of participants with any unscheduled health-seeking events for any cause and/or hospital admission for any cause since D8 follow-up at D29 follow-up	iii. The proportion of patients cured (defined as caregiver reported recovery from illness) by D8 and D29. iv. The proportion and duration of inpatient admissions (by D8 and D29) v. The proportion of patients undergoing a non-study related diagnostic test (including CXR, blood tests, urine tests, microbiological assays) on D1, and for those admitted on D1, tests conducted up until D8. vi. The proportion of deaths of any cause by D29. vii. The proportion of participants with any unscheduled health seeking events for any cause and/or hospital admission for any cause since D8 follow-up (at D29 follow-up)
	2.2 To investigate tuberculosis in the context of acute pneumonia by: i. Determining the proportion of children in the TB substudy with confirmed, unconfirmed or unlikely intrathoracic TB according to the Classification of Intrathoracic Tuberculosis Case Definitions ii. Comparing specific LUS (and mediastinal US, if done) abnormalities that may distinguish TB from non-TB lung disease. iii. Comparing LUS to both CXR and computer aided detection (CAD) of CXR as potential alternate imaging modalities, and within TB Treatment Decision Algorithms	**2.2** Endpoints related to tuberculosis in the context of acute pneumonia include: i. The proportion of children with confirmed, unconfirmed or unlikely intrathoracic TB who were enrolled in the TB substudy ii. The ability of LUS (and mediastinal US, if done) to distinguish TB from non-TB disease iii. The diagnostic accuracy of LUS compared with CXR and CAD, and within the context of TB Treatment Decision Algorithms
	2.3 Estimate the cost-effectiveness of integration of LUS into current IMCI-based management guidelines for pneumonia	**2.3** Cost-effectiveness of integration of LUS into current IMCI-based management guidelines for pneumonia
	Exploratory objectives	**Exploratory endpoints**
	3.1 To compare, where available, the aetiological diagnoses (e.g., pulmonary tuberculosis, RSV bronchiolitis, confirmed bacterial pneumonia) between the intervention and control group	**3.1** Proportion of different aetiological diagnoses (e.g., pulmonary tuberculosis, RSV bronchiolitis, confirmed bacterial pneumonia).
	3.2 To assess the effect of the intervention (when compared to routine care) in children with WHO IMCI clinical pneumonia on: i. the duration of antibiotic treatment between D1 and D8 ii. the proportion of participants with a change in antibiotic treatment strategy by D8 (including class switching, extension of spectrum)	**3.2** Evaluation of the effect of the intervention in children with clinical pneumonia on: i. The number of days of antibiotic treatment received between D1 and D8 ii. The proportion of children with a change in antibiotic treatment strategy by D8 (including class switching, switching of agent, extension of spectrum).
	3.3 To assess the diagnostic and risk stratification potential of LUS and Lung Auscultation (LAusc) in comparison to clinical signs and symptoms, CXR and host biomarkers.	**3.3** Proportion and type of abnormalities detected in LUS and LAusc and their retrospective predictive performance (compared to clinical signs and symptoms, CXR and host biomarkers as available) in the diagnosis and risk stratification of pneumonia.
	3.4 To evaluate a LUS severity score in a cohort of patients with clinical pneumonia for risk stratification.	**3.4**The ability of a clinical LUS severity score in stratifying risk in a cohort of patients with clinical pneumonia.

	3.5 To improve current risk stratification and management guidelines for clinical pneumonia, including improved LUS feature thresholds to guide antibiotic prescription	**3.5** Improved risk stratification and management guidelines for clinical pneumonia through the inclusion of improved LUS feature thresholds and novel and personalized biomarkers.
	3.6 To explore new generation host biomarkers and transcriptome signatures to identify patients with bacterial pneumonia or to predict adverse outcomes.	**3.6** Identification of differential host biomarker and transcriptomic expression patterns distinguishing bacterial pneumonia and predicting adverse outcomes.
	3.7 To develop a flexible and interpretable multimodal deep learning algorithm to automate the interpretation of clinical signs (including LUS) and symptoms for the diagnosis and risk stratification of pneumonia.	**3.7** Identification of the various definitions of pneumonia (clinical, IMCI, expert LUS, retrospective diagnosis) using a deep learning algorithm using LUS (with and without other clinical variables).
	3.8 To optimize the diagnostic and risk-stratification pathway by identifying the most predictive combination, order, and number of variables.	**3.8** Stratification of disease severity using a deep learning algorithm using LUS (+/- other clinical variables)
	3.9 To review the LUS features detected on blinded retrospective expert LUS analysis in the control group	**3.9** Proportion and type of abnormalities detected on LUS on blinded retrospective expert LUS analysis in control group.
	3.10 In children enrolled in the TB substudy: i. To assess the role of novel biomarkers in the diagnosis of TB in children ii. To assess the proportion with sole or concomitant extrapulmonary TB	**3.10** In children enrolled in the TB substudy: i. The role of novel biomarkers in the diagnosis of TB in children ii. The proportion with sole or concomitant extrapulmonary TB
Study Intervention	**IMCI-Point of Care Lung Ultrasound algorithm (IMCI-PLUS)** The intervention will integrate LUS into current management guidelines for pneumonia (national guidelines based on IMCI). Patients will receive LUS on the day of enrolment and clinicians will be provided guidance on the interpretation of the findings and the implications on antibiotic prescription. Additional guidance regarding admission or site of care will not be provided and will be based on local/national guidelines based on IMCI as per routine care.	



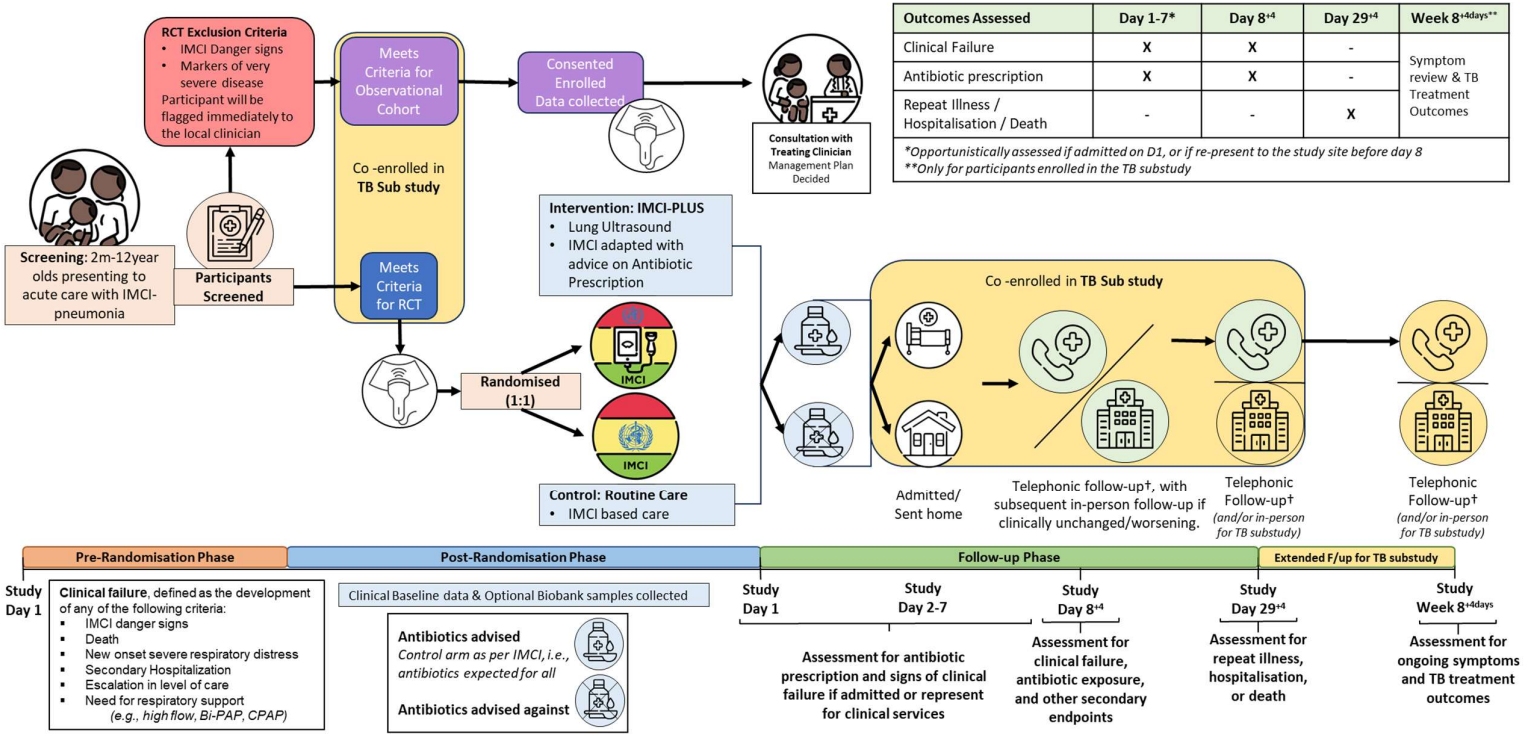
** Definitions as per WHO IMCI, South African/Tanzanian/Senegalese Standard Treatment Guidelines, except:*

- *HIV exposed, and HIV positive patients older than 12months controlled on treatment, will not be classified as severe/very severe (if not meeting other criteria for severe disease).*

*** Please note, the class and dose of antibiotic prescribed will be decided by the treating health care provider in line with local guidelines.*

<u>For admitted patients:</u>
Those in the intervention group with clinical deterioration will have a repeat LUS performed to assess for new evidence of consolidation in patients without antibiotics and to assess for additional/severe complications in those on antibiotics. Guidance will be provided for the interpretation of the findings in line with the table above. Those with "poor response" to 1st line therapy at 72hours (lack of improvement of respiratory distress, persistence of fever >38ºC) will have a repeat LUS performed and interpretations & guidance on management of complications provided in line with the table above.

<u>For non-admitted patients:</u>
All participants will be advised to re-present to the healthcare facility (i.e., the study site) for repeat review as per the IMCI framework in the case of clinical deterioration or persistence of symptoms >3 days. If an in-person visit on approximately Day 3 is standard-of-care at the site for children with IMCI-

	pneumonia, then this visit will be conducted at the study site by the research team. Transport costs will be re-imbursed to ensure access to care for families in case of clinical deterioration. Those in the intervention group with clinical deterioration will have a repeat LUS performed to assess for new evidence of consolidation in patients without antibiotics and to assess for additional/severe complications in those on antibiotics. Guidance will be provided for the interpretation of the findings in line with the table above.
Control Group	The control group will be managed by the treating clinician as per routine care. Routine care in South African, Tanzanian, and Senegalese District/Regional Hospitals are as per the Standard Treatment Guidelines which is based on IMCI (see last column in the table above). These guidelines recommend antibiotic prescriptions for all cases. In South Africa, despite slight local differences between provinces, recommended investigations include a chest X-ray and a blood culture for those classified as having "Very Severe Pneumonia". No other investigations are advised for any other group. In Tanzania, recommended investigations include a full blood count, arterial blood gas, C-reactive protein, and chest X-ray, depending on availability. The same follow-up instructions (return in case of clinical deterioration or persistence of symptoms >3 days) will be given to non-admitted patients. If an in-person visit on approximately Day 3 is standard-of-care at the site for children with IMCI-pneumonia, then this visit will be conducted at the study site. Refresher training on current local treatment guidelines will be provided prior to the start of the study.
Study Flow / Overview	 † If uncontactable, alternate strategies such as home-visits will be considered

Study Design	This is a prospective, open label, individually randomised controlled trial (RCT) with two arms (intervention and control) investigating Lung Ultrasound (LUS) as a novel tool for the management of WHO clinical pneumonia in outpatient and emergency room settings
Statistical Considerations	Statistical analysis will be performed by the trial statistician using R or Stata. Analyses will follow CONSORT guidelines and intention-to-treat (ITT) principles. A flowchart will describe the inclusion and follow-up of participants by study arm. Baseline characteristics will be described by study group with summary statistics such as median and interquartile range or number and percentage; no formal testing between groups will be performed. Outcomes will be described by group using summary statistics. The first primary outcome, the proportion of children receiving antibiotics on D1, will be assessed for superiority on both the ITT and per protocol sets using a logistic regression model, reporting odds ratios and a modified Poisson regression reporting risk ratios and risk differences and their respective 95% confidence intervals (CI). The second primary outcome, the proportion of children with clinical failure by D8, will be evaluated using a CI approach. A figure illustrating the CIs of the risk difference and the non-inferiority margin will be presented. Primary analyses for the non-inferiority comparison will be performed on both the ITT and per protocol sets. If clinical failure in the intervention group is found to be non-inferior to the control, then we will assess for superiority using the ITT set. All models will be adjusted for the stratification factors of site and age group. Binary secondary outcomes with sufficient events will be evaluated in the same way as the primary superiority outcome. Rare outcomes such as death will be compared across arms using non-parametric or small sample tests. The secondary outcomes of duration of hospitalization will be tested non-parametrically using a Wilcoxon rank-sum test. Further details will be provided in the statistical analysis plan, including approaches for the primary outcomes analysis under the estimands framework.
Inclusion- / Exclusion Criteria	**Inclusion Criteria:** Children aged ≥60 days to <13 years presenting for acute care to a study site with WHO IMCI clinical pneumonia, defined as: 1. Cough OR Difficulty Breathing **AND**, 2. One of the below: 2a. Fast breathing (tachypnoea) ▪ > 50/minute (≥60 days <1 year) ▪ > 40/minute (≥1–<5 years) ▪ > 25/minute (≥5-<13 years) **OR** 2b. Lower chest wall indrawing **Exclusion Criteria:** 1. Presenting for repeat visit/follow-up of a treated lower respiratory tract infection (index illness / non-acute) or enrolled in the study within the preceding 28 days. 2. Currently taking antibiotic treatment for more than 48 hours at the time of enrolment 3. WHO IMCI danger signs (*inability to drink/breastfeed, vomiting everything, convulsions with this illness, lethargy/unconscious*) 4. Presence of jaundice 5. Hypoxaemia with SpO2<88% 6. SpO2<90% (*or country-specific / altitude-adjusted thresholds*): o With signs of severe respiratory distress (*such as nasal flaring, grunting, etc.*) **OR** o In children < 6 months 7. Requiring non-invasive ventilatory support (*i.e., high-flow, bi-PAP, CPAP*) 8. Underlying disease associated with increased risk of severe pneumonia or pneumonia of unusual aetiology *(e.g., WHO acute malnutrition requiring antibiotics as per local guidelines, severe immunodeficiency*) 9. HIV positive participant that is either: o less than 12 months old, **OR** o requiring admission for this illness,

	OR ○ known to be uncontrolled on treatment (with a documented VL >1000c/ml in the previous 6 months) 10. Caregiver unavailable at the time of enrolment, or unwilling, to provide informed consent Children meeting all inclusion criteria, but meeting exclusion criteria 1-9, will be enrolled in an observational component of the study to obtain a more detailed understanding of all children presenting with IMCI pneumonia and in the TB substudy (See section 5.5 and 5.6).
Number of Participants with Rationale	With an assumed baseline proportion of clinical failure in the control group of 5% and using an acceptable clinical difference of 1.5x as a non-inferiority margin (therefore a delta of 2.5%) [1–5], the estimated sample size required across all sites would be 2730 (power 85%). This would equate to 1365 participants per group for the co-primary endpoints. We however aim to enrol a total of 3000 participants under the age of 5 years of age (power >85%) as this is the age group of greatest interest based on the current IMCI framework. However, due to limited data on paediatric pneumonia outcomes in the 5-12years age group we wish to include these children as well. Considering approximately 90% of children presenting for acute respiratory care in the age group ≥60days-<13years are <5years, we would aim for a total sample size of 3500 participants, 1750 participants per group, to account for repeat visits of the same child within the enrolment period as well as potential differences in clinical failure rates between sites. We will conduct an interim analysis assessing, among other things, LTFU and clinical failure rates. This will be done approximately 25% through the RCT and the sample size adjusted accordingly if appropriate. The planned breakdown of participant enrolment per country is as follows: Tanzania – 2000 participants, Senegal – 500 participants, South Africa – 1000 participants. As the expected difference in antibiotic prescription rates is expected to be large, this sample size will provide sufficient power to test for a clinically meaningful difference of 20% on Day 1 and 15% by Day 8 (secondary outcome).
Study procedures	**Patient Enrolment** All consecutive paediatric patient (≥60 days to <13 years) presenting to the acute outpatient department of a study site during study operating hours will be screened for participation. Only patients meeting all the inclusion and none of the exclusion criteria will be recruited into the RCT. **Data Collection** Study staff will capture all clinical, diagnostic (including LUS findings), and management data on the day of enrolment (D1). Subsequent clinical, diagnostic, and management data from planned and unplanned study visits, will also be collected. All data will be recorded in an eCRF in REDCap®. **Lung Ultrasound** LUS will be performed using a standard point of care device with CE marking by trained study staff impartial to the management of the participant. A standardised image acquisition and documentation protocol will be followed: • On participants: ○ ≥60 days - <5 years - a 8-point sliding acquisition protocol with 2 costophrenic angle views will be used ○ ≥5 years- <13 years – A 8-point sliding acquisition protocol with 2 costophrenic angle views will be used which includes apical sites for improved tuberculosis (TB) detection • Both of the above ensure adequate coverage of the anterior and posterior apexes, anterior superior, anterior inferior, posterior superior, posterior inferior and lateral thoracic regions. • At selected sites, depending on the availability of an appropriate small footprint US probe, additional mediastinal views will be collected for the identification of intrathoracic lymph nodes. **Sample Collection and Storage for retrospective testing** Subject to a separate consent form, and depending on site feasibility and participant consent, one or more of the samples below will be collected for storage and retrospective testing. These samples may include: • Nasopharyngeal swab sample (Flock swab in UTM tube) • Saliva sample • Maximum 1mL blood sample

We will use topical anaesthetic cream and distraction techniques where possible to minimise distress. Where a participant will require blood sample collection for their routine care, and where appropriate, the collection of the study samples will coincide with this to minimize the number of blood draws required.

Follow-up

Outcomes will be assessed through review of their available clinical records (paper record or electronic health record) and standardised patient assessment forms from the study site. For inpatients, daily record review will be conducted along with a D8 follow-up. For outpatients, treatment will be reviewed at enrolment, at unplanned follow-up visits (in person), and at D8 follow-up. The assessments will include:

- Antibiotic-related assessment
  - Data on antibiotic prescription, duration, type, dosage, and route of administration.
- Event-related data
  - Clinical failure

On D8, a telephone follow-up will be conducted with the caregiver to assess for current health status, evidence of clinical failure, clinical course since enrolment, and antibiotic use. If caregivers cannot be reached by phone, other strategies will be implemented to reach these caregivers, including home visits, and establishing contact through community stakeholders (community leaders, community health workers). Based on responses, participants may be flagged for in-person review and advised to return to their health facility/study site for clinical review. Participants will be compensated for transport related costs relating to this repeat visit.

Returning participants will be triaged as per routine outpatient presentation and study staff will assist in screening them for signs of clinical failure. If the participant meets WHO danger sign criteria / signs of severe disease, they will be immediately referred to a hospital clinician. A repeat LUS will be performed for all returning patients with persistent symptoms on D8 and these children will also be enrolled, with informed consent, into the TB substudy.

Unscheduled follow-ups before will be managed as per the D8 in-person visit outlined above and as per standard guidelines. However, as per the intervention strategy, those in the intervention group with clinical deterioration will have a repeat LUS performed to assess for new evidence of consolidation in patients without antibiotics and to assess for additional/severe complications in those on antibiotics. These children will also be enrolled, with informed consent, on the TB substudy. Guidance will be provided for the interpretation of the findings in line with IMCI-PLUS algorithm.
On D29, a telephone follow-up will be performed to assess for repeat health seeking events for a respiratory illness, hospitalisation, history of starting TB treatment, and death. All children with persistent or recurrent respiratory illness at D29, as well as those reporting TB exposure or starting TB treatment in routine care, will be reviewed in-person and enrolled, with informed consent, into the TB sub study.

Observational Cohort Study

Patients screened at the facility who meet all inclusion criteria but also meet any exclusion criteria numbers 1-9 (and will therefore be excluded from the RCT), will instead be recruited into an observational cohort study to obtain a more detailed understanding of all children presenting with IMCI pneumonia. These participants will be consented on a separate consent & assent form as appropriate and receive a separate patient information sheet. All above procedures will apply (including data collection, LUS and LAusc collection, sample collection, clinical outcomes assessment on D1, and clinical data related to any admission). Participants will have LUS collected at all in-person engagements but not interpreted at the time of the visit. Participants will however **not** be randomised and will not receive the study intervention. Participants will also receive a D8 and D29 telephone follow-up.

Inclusion into the TB Substudy

The following patients will be eligible for enrolment in the TB substudy with some variation in implementation of these inclusion criteria expected between institutions. Site-specific details and procedures will be clearly outlined in each site's Manual of Operations:

- Children in the Observational Cohort Study (Section 5.5)
- Children in the RCT:
  - < 2years, and/or living with HIV, and/or with recent TB exposure at D1

	• with clinical failure at D8 or persistent/recurrent symptoms at D29 • with TB exposure or TB disease diagnosis during the study period These children will be recruited into the TB substudy with the aim of meeting the secondary trial objectives. These children will be specifically consented either on a separate consent form or on a separate section of the observational cohort consent form depending on their point of entry into the substudy. They will not be randomised unless they are also enrolled in the main trial but they will have all procedures outlined for the main trial and the observational cohort as well as the following additional tests: • Collection of at least 1 respiratory sample (gastric aspirates and/or induced sputum and/or nasopharyngeal aspirates) for Xpert Ultra MTB/RIF testing and liquid culture • Urine for lateral flow lipoarabinomannan (LAM) if living with HIV and/or SAM and available at the site • CXR (both anteroposterior and lateral), if done as an investigation in the routine care pathway, for real-time interpretation by clinicians to facilitate appropriate clinical care and for archiving for retrospective interpretation with CAD software • Collection of between 1.5mL and 6mL venous blood for storage and retrospective TB biomarker testing All children enrolled in the TB substudy will be linked to care within the routine care setting as appropriate and all will have telephonic follow-up visits with the study team on D8 and D29 as well as an additional telephonic/in-person follow-up at week 8 (Week 8 in-person follow-up would be at the discretion of each site based on available resources). If caregivers cannot be reached by phone for follow-up visits, other strategies will be implemented to reach these caregivers, including home visits, and establishing contact through community stakeholders (community leaders, community health workers). Participants will have LUS collected at all in-person engagements but not interpreted at the time of the visit. If there are persistent or recurrent symptoms an in-person visit will be undertaken to ensure appropriate linkage to care for re-investigation for TB. In-person visits will also take place if any sample test positive for TB or if a child is started on TB treatment in routine care (to allow the study team to evaluate for treatment response and classification according to the standard NIH TB case classifications).

Time since enrolment (days)	D1	D1	D2-7*	D8	D29	Week 8
Visit	*Enrolment*	*Clinical Visit*	*Unscheduled in-person Follow-up*	*1st Follow-up (telephone/ in-person)*	*2nd Follow-up (telephone/ in-person)*	*3rd Follow-up (telephone/ in-person)*
Windows				+4days	+4 days	+4days
Enrolment						
Eligibility screening	+					
Informed consent	+					
Demographic data collection	+					
Baseline clinical data collection	+					
LUS	+		+**	+^	+^	+^
LAusc	+					
Randomisation	+					
Sample collection		+	+^^	+^^	+^^	+^^
Interventions						
Control group: Routine care		+	+			
Intervention group: IMCI-PLUS algorithm and guidance for clinical deterioration & persistence of symptoms		+	+			
Assessments						
Antibiotic-related assessment		+	+	+		
Event-related data (Clinical Failure)			+	+	+	
Clinical signs	+	+	+	+^	+^	+^
Clinical management		+	+	+^	+^	+^
Survival			+	+	+	+
Adverse Events		+	+	+		
TB substudy only – Symptoms and TB exposure and/or treatment history				+	+	+

For more detail regarding data points collected for Primary and Secondary outcomes, see Section 5.3.1

* *D2-7 refers to unplanned follow-up as a result of participants representing to the study site for the index illness AND/OR scheduled study visit for those sites where follow-up is routine care*

** *LUS performed at D2-7 follow-up visit if participant is:*

- *in the intervention group and clinically unchanged/ worsened*
- *in the control group where possible/feasible*

^ *Only collected if in-person follow-up*

^^ *Sample collection after the D1 visit for the TB substudy only, in line with details in Section 5.6*

Study Duration and Schedule	The study will aim for a maximum recruitment period of 24 months with an initial pilot phase. Each participant included will be followed up for a total of 28 days after enrolment. Those in the TB substudy will be follow-up for a total of 8 weeks from the point of enrolment into the TB substudy.
	Multi-site study

Study Centre(s)	Ehlanzeni District, Mpumalanga, South Africa: District/Regional Hospital and feeder clinics Western Cape, South Africa: District/Regional/Tertiary Hospital and feeder clinics	Dar Es Salaam, Tanzania: Temeke Hospital and surrounding feeder clinics within the Temeke Region Dakar, Senegal
Data privacy	Subject confidentiality is ensured by using subject identification code numbers corresponding to data in the computer files. Applicable laws and regulations will be adhered to, including but not limited to the General Data Protection Regulations (GDPR) and Protection of Personal Information Act 4 of 2013 (POPIA), pertaining to the use, transfer, processing and storage of Data Some identifying information (contact information) needs to be collected, but this information will only be available to study staff in direct need of it to perform study related tasks (e.g., contact information available to the person in charge of phone interviews), and will be removed from the data extracts used for data monitoring and analysis. Biological material in this study is not identified by participant name but by a unique participant number. Biological material is appropriately stored in a restricted area only accessible to the authorised personnel. The Sponsor investigator ensures that traceability of the samples and data is possible to enable participant withdrawal	
Risk / Benefit Assessment	The use of LUS may lead to better targeting of children in need for antibiotic treatment. This reduction in antibiotic treatment is expected to reduce side effects for patients and antimicrobial resistance, which is a major global health problem. The risk of the intervention is judged as comparable to standard medical care. The proposed intervention is based on previously validated tests. The risks of this study are minimal. A potential risk is related to a participant with bacterial pneumonia not receiving an antibiotic. However, there are several layers of safety included in the study design to mitigate this risk: • Eligibility criteria have been carefully selected to only include children that may truly benefit from the intervention. Patients with very severe symptoms requiring close inpatient monitoring are excluded. Patients with a higher baseline risk for bacterial pneumonia (immunodeficiency, severe acute malnutrition) will be excluded. • Systematic clinical outcome assessments and safety monitoring will be undertaken (including the establishment of an Independent Data Monitoring Committee for regular review of cumulative safety and study conduct data, see Section 0).	
Ethical consideration	The use of LUS may lead to the better targeting of children in need for antibiotic treatment. This reduction in antibiotic treatment is expected to reduce side effects for patients and antimicrobial resistance, a major global health concern. The risk of the intervention is judged as comparable to standard medical care with minimal associated risk. Though LUS is increasingly used in the management of clinical pneumonia in children, its additional benefit has not been rigorously studied. This is particularly relevant in IMCI settings, where additional diagnostics must demonstrate potential clinical benefit before integration into current management guidelines is considered. The inclusion criteria were chosen based on the current IMCI framework, allowing for interpretation (including generalizability) within the IMCI framework. Exclusion criteria were carefully chosen to ensure the most vulnerable of patients were not enrolled. Randomization of participants is necessary since there is currently no diagnostic reference standard for bacterial pneumonia (e.g., a reference standard for the need for antibiotic treatment) and diagnostic accuracy studies for LUS against other reference standards (e.g. radiography or lab investigations) are of limited use	
Regulatory Aspects & Safety	This study is conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the HRA as well as other locally relevant legal and regulatory requirements. The study will be conducted in accordance with the principles of Good Clinical Practice (GCP)	

2 STUDY ADMINISTRATIVE STRUCTURE

Sponsor Representative, Overall Coordinating Investigator
Kristina Keitel

Co-Principal Investigators
Jacques du Toit
Stephen Tollman
Karim Manji
Nahya Salim Masoud
Megan Palmer
Niel van Hoving
Papa Moctar Faye

Other Investigators
Details of site investigators, sub-investigators, and delegated study staff are maintained in the site-specific delegation of duties logs and associated regulatory documents, which are updated as needed and filed in the Investigator Site File.

Statistician
Tracy Glass

Monitoring institution
Swiss TPH

Independent Data Monitoring Committee (IDMC)
The responsibility of the Independent Data Monitoring Committee (IDMC) will be to safeguard the interests of trial participants, assess the safety of the interventions during the trial, and contribute to monitoring the overall conduct of the clinical trial. The IDMC is independent of, but reports to, the trial coordination group. The specific roles of the IDMC are to monitor evidence for treatment harm (e.g., Serious Adverse Events (SAEs)), recommend whether the trial should continue to recruit participants or whether recruitment should be stopped due to safety reasons. The trial statistician or a named independent delegate will produce the report to the IDMC and will participate in IDMC meetings. Further details of IDMC functioning and procedures will be provided by the Sponsor Representative in the IDMC Charter agreed and signed by all IDMC members.

Study Coordination Group will be formed comprising the Sponsor Representative, other lead investigators, study statistician, and study managers. The coordination group will provide oversight over the study and coordinate study activities. Among other tasks, it will monitor recruitment figures and losses to follow-up and decide on major protocol modifications. The ultimate decision for the continuation of the trial lies with the coordination group.

A **Technical Advisory Panel** (TAP) will be formed and comprise expertise in childhood pneumonia, clinical trials, and policy. Among other tasks, the TAP will give advice on the protocol, recruitment, and major protocol modifications. The TAP will also be involved in data analysis, publication, and dissemination.

3 BACKGROUND AND RATIONALE

In 2019, lower respiratory tract infections (LRTI) caused 2.6 million deaths worldwide, making them the fourth leading cause of death overall [6]. While the statistic is global the effect is concentrated in low-resource settings and among children, with pneumonia being the single largest infectious cause of death in children worldwide [7].

LRTI (including pneumonia) are the most common reason for sick children to present for acute outpatient care and current best practice pneumonia management guidelines advocate for all cases to receive a course of antibiotics. This relies on the World Health Organization's (WHO) Integrated Management of Childhood Infections (IMCI) guidelines, first developed in the 1990s - a time when providing access to antibiotics was a major goal for public health programs [8]. Today, antibiotics are readily available in most countries in sub-Saharan Africa (SSA) and antibiotic over-prescription has become a public health crisis[9]. The IMCI framework was re-iterated in 2014 but still rely on presumptive treatment based on clinical signs alone (cough and/or difficulty breathing, respiratory rate, and lower chest wall indrawing) [8], as evidence to include additional diagnostic tests into the IMCI approach has been lacking. However clinical features inadequately distinguish bacterial infections and complications from common, self-limiting viral infections[10]. Furthermore, recent evidence estimates the incidence of bacterial respiratory infections in SSA, using a combination of microbiology, chest x-ray (CXR), and clinical outcomes as reference standards, is as low as 2-4% in primary[11,12], and 23.3-31.6% in secondary[13], care. Therefore, approximately 9 out of 10 courses of antibiotics recommended by current guidelines for children with LRTI are estimated to be unnecessary.

Bacterial antimicrobial resistance (AMR), responsible for 1.27 million deaths in 2019 and with the highest burden in SSA[14], is thus of increasing concern; with nearly as many deaths as malaria and HIV combined. Inappropriately and excessively prescribing antibiotics represents one primary contributor of bacterial AMR[15–17]. In SSA, more than 50% of children who are sick receive antibiotics when visiting health facilities[18–23] - with 80–90% of such antibiotics prescribed at the outpatient level [24] and most deemed inappropriate[18,24]. Most inappropriate antibiotic use occurs with respiratory infections due to systematic overprescription as outlined above[18,24]. Antibiotic use and AMR are projected to increase over the next years, indicating urgent action[25–27]. Accordingly, WHO declared AMR as "one of the biggest threats to global health, food security and development today."[9]. Effective solutions to improve antibiotic stewardship for childhood infections in SSA primary care settings remain lacking, though its well recognized improved diagnostic and management processes are essential.

Lacking more effective tools to safely identify the minority of children requiring antibiotics, frontline clinicians in low resource settings therefore prescribe antibiotics to nearly every child, driving the above-described overuse and fuelling local AMR, whilst significantly overtreating cases of viral pneumonia[10]. Besides the risk of AMR at the population level, reducing antibiotic prescriptions is also important for each individual patient. Antibiotic exposure early in life has been associated with an increased risk of health conditions, including asthma, allergic rhinitis, atopic dermatitis, autoimmune disease, obesity, and neurodevelopmental disorders[28]. Improving IMCI diagnostic criteria to better identify children with pneumonia that would benefit from antibiotic therapy is therefore a WHO research priority.

Several tools have since been proposed (currently at different stages of diagnostic development) to both improve diagnostic pathways and improve appropriateness of antimicrobial prescriptions in LMICs. These include the use of point of care C-reactive Protein (CRP), Procalcitonin (PCT), comprehensive electronic decision support algorithms [11,29,30], and more novel applications of established technologies. Two such technologies are Lung Ultrasound (LUS) and Lung Auscultation (LAusc). LUS is a well-established, near consumable-free, and non-invasive point-of-care respiratory exam. While LUS is less ubiquitous than the stethoscope, it's new portable and affordable ultrasound-on-a-chip design, pluggable into a

mobile device, has the potential to be integrated into the standard clinical exam without incurring extra costs, time, radiation, or specialist consultation. These portable ultrasound devices have reached regulatory approval and are used in medical care across SSA. This together with increasing evidence showing its ability to effectively detect lung consolidation in pneumonia have made it an increasingly attractive tool for frontline clinicians; already becoming an established practice in the outpatient case management of children with respiratory infections in many high-resource settings[31–33] as well as growing steadily in popularity in SSA[34].

A number of studies have compared LUS to CXR and/or Computerised tomography (CT) for pneumonia diagnosis. A multi-centre trial in Europe including 362 adult patients with pneumonia compared LUS performed by a specialist to a diagnosis of pneumonia made by CXR and in some cases CT. The authors reported a sensitivity of 93.4% (95% Confidence Interval (CI) 89.2-96.3%) and a specificity of 97.7% (95%CI 89.2-99.6%) [35]. Most studies in children (performed primarily in high-income countries and tertiary care settings) have found high diagnostic accuracy when comparing LUS to CXR, using either CXR, CT, or Magnetic Resonance Imaging (MRI) as reference standards, with a recent meta-analysis suggesting an overall sensitivity of 95% (91-97%) and specificity of 96% (90-99%) [36,37]. A smaller number of studies have investigated using LUS to assist in determining the etiological causes of the consolidations[38,39]. Although these have shown a possibility of differentiating viral from bacterial infections, the reference standards used were nasopharyngeal swab carriage, clinical syndromes, and other clinically available data. A notable limitation of this study was therefore the lack of a microbiologically confirmed diagnosis, making it hard to make definitive statements about the ability of LUS to differentiate. This lack of reliable reference standards in paediatric pneumonia is a well-documented challenge, most notably discussed in the Pneumonia Etiology Research for Child Health (PERCH) study, and thus limits the value of etiology focused diagnostic accuracy studies [13,40,41]. Although the first studies on the use of LUS to detect lung consolidation in children in LMICs are promising, as seen in Nepal, Peru, and Egypt [42–46], they remain limited in scope and context, with no evidence on the clinical impact of LUS assisted diagnoses on antimicrobial use or health outcomes, particularly in a primary care setting. This highlights the importance of the assessment of LUS integrated into care to assess for real changes in treatment outcomes through an interventional study, rather than observational diagnostic accuracy studies.

Studies assessing the potential of LUS in the diagnosis of pulmonary tuberculosis (TB) in children are equally limited [36]. With paediatric TB diagnosis remaining a huge challenge in low resource settings, many cases still remain undiagnosed and untreated – an issue being addressed though the development of pragmatic TB Treatment Decision Algorithms for settings with and without CXR. These Treatment Decision Algorithms are now included in the operational handbook accompanying the WHO guidelines on the management of TB in children and adolescents[47]. More evidence is however needed on the potential role of LUS as an alternative diagnostic modality in the context of these TB Treatment Decision Algorithms.

Regarding operability of LUS in SSA by novice health workers, LUS performance evidence shows it is possible to capture images/video with minimal training and achieve high diagnostic quality, as evidenced in both South Sudan and Bangladesh[48–50], though concerns remain regarding diagnostic quality outside research settings[49,50]. Image acquisition aside, interpretation and inter-user bias remain the largest concern, this however makes them excellent candidates for automated interpretation by objective computer-aided pattern detection. Using deep learning our collaborating team at École Polytechnique Fédérale de Lausanne (EPFL) have found excellent preliminary results in Swiss cohorts, matching and out-performing expert evaluation for risk stratification (Area Under the Receiver Operating characteristic Curve (AUROC) >80%) and diagnosis (AUROC >90%) of COVID-19 pneumonia (unpublished data).

As with LUS, LAsuc is another established tool being applied in a novel way. While evidence for the potential of LAusc for paediatric pneumonia is limited, some preliminary evidence on the predictive capacity of other respiratory sounds is emerging; for instance, the application of deep learning was able to predict diagnosis from breath and cough sounds collected on a mobile application with an AUC of around 80% [51]. Another group achieved above 95% sensitivity and specificity on discriminating COVID-19 coughs from other pathologies as well as healthy patients[52]. A study in South Africa included 33 culture-confirmed TB patients with healthy controls and found a diagnostic accuracy of 75%[53]. This doesn't however speak much to the more pressing question of differentiating TB from non-TB pneumonia. While these are extremely promising results, no such trials have been performed in TB endemic areas, particularly challenging the specificity of LAusc for the detection of either pneumonia or TB. There is also as yet no regulatory approval for the use of AI powered LAusc devices in clinical practice.

This study therefore seeks to enable adoption of LUS into the routine management of IMCI clinical pneumonia through addressing key evidence gaps for translation into policy and practice, which includes generating evidence on the possible impact on health outcomes, namely: Does the integration of LUS into IMCI-based management guidelines better identify those children that would most benefit from antibiotic treatment, thus reducing antibiotic overuse without compromising health outcomes?

4 STUDY OBJECTIVES AND DESIGN

4.1 Hypothesis and primary objective

The overall purpose of this study is to assess whether the integration of Lung Ultrasound (LUS) into current IMCI based management guidelines for pneumonia can improve targeting of antibiotic treatment for those with a higher probability of bacterial pneumonia, thereby mitigating antimicrobial resistance and improving health outcomes.

> *We hypothesise that the integration of lung ultrasound (LUS) (including standardised interpretation) into the IMCI-based management guidelines of clinical pneumonia will better identify those who would benefit from antibiotic treatment, which will lead to a reduction in antibiotic overuse without compromising health outcomes.*

Primary Objective

The primary objective of this study is to evaluate whether the integration of LUS into current IMCI-based management guidelines for pneumonia (intervention group):

(1.1) Reduces antibiotic treatment at D1
(1.2) Is non-inferior in terms of clinical failure by D8.

among children aged ≥60 days - <13 years with WHO IMCI clinical pneumonia, when compared to routine care (control group).

Related Hypotheses:

(1.1) The addition of LUS into management guidelines for pneumonia (intervention group) decreases the proportion of children with WHO IMCI clinical pneumonia that receive an antibiotic on D1 when compared to routine care (control group).
(1.2) The integration of LUS into management guidelines (intervention group) is non-inferior to routine care (control group) in terms of clinical failure by D8.

Secondary Objective

(2.1) To assess the effect of the intervention (when compared to routine care) in children with WHO IMCI clinical pneumonia on:

i. the proportion of children prescribed antibiotics by D8

ii. the proportion of adverse drug reactions related to routine antibiotic treatment by D8 (i.e., Anaphylactic reaction, severe diarrhoea, or generalised severe rash).
iii. the proportion of participants cured (defined as caregiver-reported recovery from illness) by D8 and D29 (for those not cured at D8)
iv. the proportion and duration of inpatient admissions by D8 and D29 (for those admitted on D1 only).
v. the use of diagnostic tests (in addition to LUS) on D1, and for those admitted, by D8.
vi. death by D29
vii. the proportion of participants with any unscheduled health-seeking events for any cause and/or hospital admission for any cause since D8 follow-up at D29 follow-up

(2.2) To Investigate tuberculosis in the context of acute pneumonia by:

i. Determining the proportion of children in the TB substudy with confirmed, unconfirmed or unlikely intrathoracic TB according to the Classification of Intrathoracic Tuberculosis Case Definitions [54]
ii. Comparing specific LUS (and mediastinal US, if done) abnormalities that may distinguish TB from non-TB lung disease.
iii. Comparing LUS to both CXR and computer aided detection (CAD) of CXR as potential alternate imaging modalities, and within TB Treatment Decision Algorithms

(2.3) Estimate the cost-effectiveness of integration of LUS into current IMCI-based management guidelines for pneumonia

Justification: *Further characterization of aetiologies will enable improvement in the IMCI-PLUS algorithm.*

Exploratory objectives

(3.1) To compare, where available, the aetiological diagnoses (e.g., pulmonary tuberculosis, RSV bronchiolitis, confirmed bacterial pneumonia) between the intervention and control group (See Section 5.3.4 relating to relevant sample collection).

(3.2) To assess the effect of the intervention (when compared to routine care) in children with WHO IMCI clinical pneumonia on:

i. the duration of antibiotic treatment between D1 and D8
ii. the proportion of participants with a change in antibiotic treatment strategy by D8 (including class switching, extension of spectrum)

(3.3) To assess the diagnostic and risk stratification potential of LUS and Lung Auscultation (LAusc) in comparison to clinical signs and symptoms, CXR and host biomarkers.

(3.4) To evaluate a LUS severity score in a cohort of patients with clinical pneumonia for risk stratification.

(3.5) To improve current risk stratification and management guidelines for clinical pneumonia, including improved LUS feature thresholds to guide antibiotic prescription.

(3.6) To explore new generation host biomarkers and transcriptome signatures to identify patients with bacterial pneumonia or to predict adverse outcomes.

(3.7) To develop a flexible and interpretable multimodal deep learning algorithm to automate the interpretation of clinical signs (including LUS) and symptoms for the diagnosis and risk stratification of pneumonia.

(3.8) To optimize the diagnostic and risk-stratification pathway by identifying the most predictive combination, order, and number of variables.

(3.9) To review the LUS features detected on blinded retrospective expert LUS analysis in the control group

(3.10) In children enrolled in the TB substudy (see Section 5.6):

i. To assess the role of novel biomarkers in the diagnosis of TB in children
ii. To assess the proportion with sole or concomitant extrapulmonary TB

Justification: These exploratory outcomes can support the discovery of new diagnostic and prognostic markers in children with clinical pneumonia. Machine learning identification of LUS pneumonia can support automated interpretation of LUS and facilitate implementation of this

tool in low resource settings where expert interpretation is not available, thus bridging healthcare provider skills gaps

4.2 Primary and secondary endpoints

Co-Primary Endpoints

(1.1) Proportion of participants prescribed antibiotic treatment on D1.
(1.2) Proportion of participants with clinical failure, defined as the development of any of the following criteria during the specified time periods after enrolment.

i. Any time before or on D8:
   - WHO IMCI danger sign (inability to drink/breastfeed, vomiting everything, convulsions with this illness, lethargy/unconscious)
   - New or worsening severe respiratory distress (such as grunting, head nodding, severe chest indrawing)
   - Secondary Hospitalization (defined as a hospitalization occurring after discharge from in-patient admission or outpatient visit) related to a deterioration of the presenting complaint on D1
   - Change in level of care (e.g., admission to intensive care unit, transfer to higher level of care)
   - Need for respiratory support (e.g., high flow nasal cannula, CPAP)
   - Death due to any medical cause (i.e., except trauma)

ii. At D8 outcome assessment:
   - Report from the caregiver of non-resolution/worsening of illness

Rationale: Antibiotic treatment is a relevant care-related outcome[55] *as we expect that the integration of LUS will result in a more targeted management approach, and hence a decrease, in antibiotic treatment. The most accurate point of assessment and largest effect is expected at the time of the initial management decision. Antibiotic treatment for the acute course of the illness is clinically interesting but subject to reporting bias and additional factors not addressed by the intervention (such as adherence to treatment guidelines and seeking of antibiotic treatment by caregivers) and so we chose to therefore assess cumulative prescription by D8 as a secondary endpoint.*

"Clinical failure" captures possible negative outcomes from delayed antibiotic prescription and over-treatment of antibiotics. It is a combination of safety and treatment failure outcomes and is based on previous intervention studies for pneumonia in low-and middle-income countries [1–5]

Secondary Endpoints

(2.1) Evaluation of the effect of the intervention in children with clinical pneumonia on:

i. The proportion of children prescribed an antibiotic by D8.
ii. The proportion of adverse drug reactions related to routine antibiotic treatment by D8 (i.e., Anaphylactic reaction, severe diarrhoea, or generalised severe rash).
iii. The proportion of patients cured (defined as caregiver reported recovery from illness) by D8 and D29.
iv. The proportion and duration of inpatient admissions (by D8 and D29)
v. The proportion of patients undergoing a non-study related diagnostic test (including CXR, blood tests, urine tests, microbiological assays) on D1, and for those admitted on D1, tests conducted up until D8.
vi. The proportion of deaths of any cause by D29.
vii. The proportion of participants with any unscheduled health seeking events for any cause and/or hospital admission for any cause since D8 follow-up (at D29 follow-up)

(2.2) Endpoints related to tuberculosis in the context of acute pneumonia include:

i. The proportion of children with confirmed, unconfirmed or unlikely intrathoracic TB who were enrolled in the TB substudy
ii. The ability of LUS (and mediastinal US, if done) to distinguish TB from non-TB disease
iii. The diagnostic accuracy of LUS compared with CXR and CAD, and within the context of TB Treatment Decision Algorithms

(2.3) Cost-effectiveness of integration of LUS into current IMCI-based management guidelines for pneumonia

Exploratory Endpoints

(3.1) Proportion of different aetiological diagnoses (e.g., pulmonary tuberculosis, RSV bronchiolitis, confirmed bacterial pneumonia).
(3.2) Evaluation of the effect of the intervention in children with clinical pneumonia on:
i. The number of days of antibiotic treatment received between D1 and D8
ii. The proportion of children with a change in antibiotic treatment strategy by D8 (including class switching, switching of agent, extension of spectrum).

(3.3) Proportion and type of abnormalities detected in LUS and LAusc and their retrospective predictive performance (compared to clinical signs and symptoms, CXR and host biomarkers as available) in the diagnosis and risk stratification of pneumonia.
(3.4) The ability of a clinical LUS severity score in stratifying risk in a cohort of patients with clinical pneumonia.
(3.5) Improved risk stratification and management guidelines for clinical pneumonia through the inclusion of improved LUS feature thresholds and novel and personalized biomarkers.
(3.6) Identification of differential host biomarker and transcriptomic expression patterns distinguishing bacterial pneumonia and predicting adverse outcomes.
(3.7) Identification of the various definitions of pneumonia (clinical, IMCI, expert LUS, retrospective diagnosis) using a deep learning algorithm using LUS (with and without other clinical variables).
(3.8) Stratification of disease severity using a deep learning algorithm using LUS (+/- other clinical variables)
(3.9) Proportion and type of abnormalities detected on LUS on blinded retrospective expert LUS analysis in control group.
(3.10) In children enrolled in the TB substudy (see Section 5.6):
i. The role of novel biomarkers in the diagnosis of TB in children
ii. The proportion with sole or concomitant extrapulmonary TB

4.3 Study intervention

The intervention consists of a patient management algorithm, including LUS. The trial intervention is named the "IMCI-PLUS" algorithm ("**IMCI-P**oint-of-care **L**ung **U**ltra**S**ound algorithm").

4.3.1 Intervention Group: Management based on Lung Ultrasound findings

The intervention will integrate LUS into current management guidelines for pneumonia (national guidelines based on IMCI). Patients will receive LUS on the day of enrolment and clinicians will be provided guidance on the interpretation of the findings and the implications on antibiotic prescription (See Table 1). Additional guidance regarding admission or site of care will not be provided and will be based on local/national guidelines based on IMCI as per routine care.

Those in the **intervention group** will be sent to the treating clinician with:
- Results of the LUS examination including interpretation
- Advice regarding whether the patient requires antibiotics (according to standard local guidelines) based on pre-defined thresholds (see Section 4.3.1.2).

- In the case of a normal LUS examination, advice against further investigations such as a chest x-ray or inflammatory blood markers (e.g., CRP / PCT) will be provided, although clinicians will be free to add additional tests if so desired.

LUS may be repeated during the acute course of the illness in admitted patients in the case of clinical deterioration or persistence of symptoms. Guidance on the use and interpretation of LUS in these patients will be provided. Refresher training on current local treatment guidelines will be provided prior to the start of the study as with the control group.

4.3.1.1 Lung ultrasound

LUS will be performed using a standard point of care device with CE marking (Figure 1) by trained study staff impartial to the management of the participant (also refer to Appendix, Section 13.1).

A standardised image acquisition and documentation protocol will be followed:

- On participants:
  - ≥60 days - <5 years - a 8-point sliding acquisition protocol with 2 costophrenic angle views will be used
  - ≥5 years- <13 years – A 8-point sliding acquisition protocol with 2 costophrenic angle views will be used which includes apical sites for improved tuberculosis (TB) detection
- Both of the above ensure adequate coverage of the anterior and posterior apexes, anterior superior, anterior inferior, posterior superior, posterior inferior and lateral thoracic regions.
- At selected sites, depending on the availability of an appropriate small footprint US probe, additional mediastinal views will be collected for the identification of intrathoracic lymph nodes.

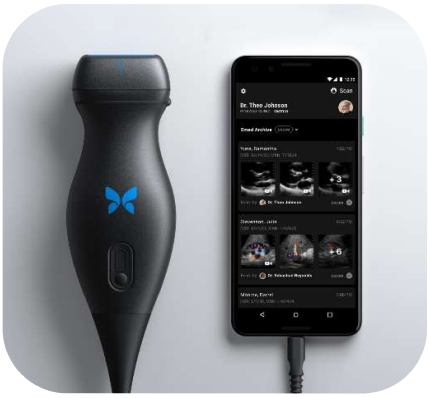


Figure 1 Example of Point of Care Ultrasound Device

4.3.1.2 Lung Ultrasound interpretations/classifications:

The study clinician performing the ultrasound will receive standardised training on image acquisition and interpretation. This will include adequate practice and examinations with support from a team of expert sonographers. Study clinicians, once confirmed to be at a suitable level of skill, will be responsible to interpret the images and provide classifications. Expert sonographers will provide back-up support to onsite research staff in case of uncertainty in the interpretation of certain images (either in person or remotely) as well as to conduct regular audits of interpretations.

Study clinicians, rather than hospital clinicians, will perform and interpret the LUS examination. This is done to 1) ensure standardisation of the acquisition and interpretation of images, 2) ensure the efficacy of LUS is assessed in a more ideal setting, as inter-user variability is a potential weakness of ultrasound and thus worth reducing for the aims of this study, and 3) acknowledge the current progress being made toward more advanced means of interpretation through the development of AI tools. This would enable the roll out of this intervention in regions with a paucity of ultrasound related expertise.

Interpretation risk categories for the likelihood of a pneumonia that would benefit from antibiotic treatment are outlined below:

1) Low:
   a. Normal artefacts (e.g., A-profile),
      AND
   b. No evidence of consolidation
      AND

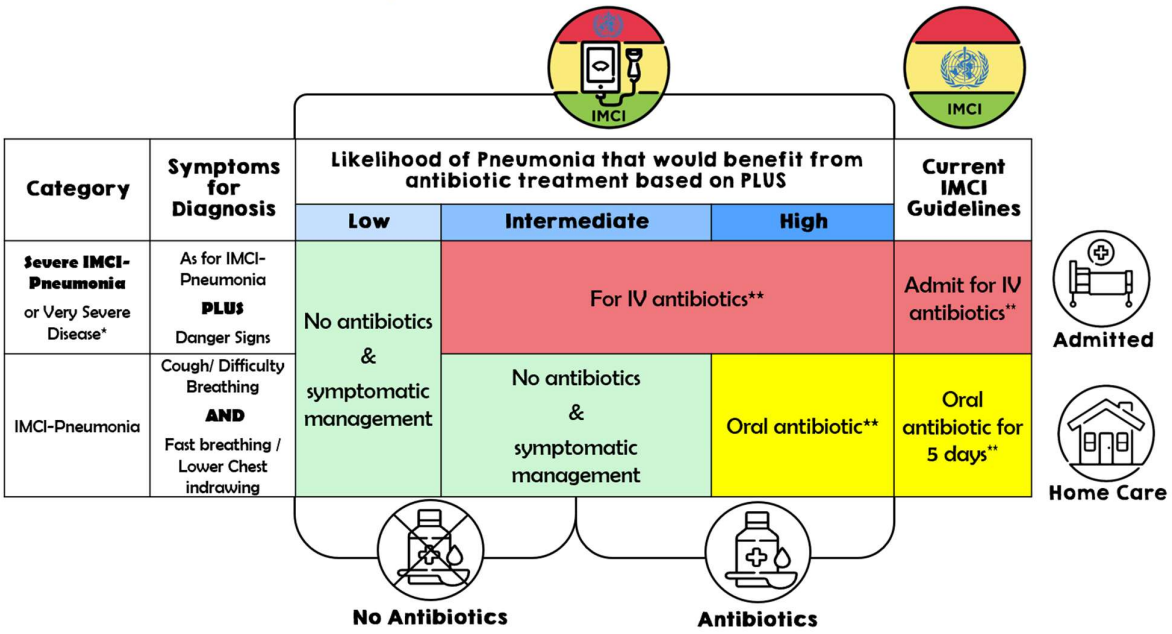
c. No complications (No effusions or cavities)

2) Intermediate:
   a. Findings compatible with a minor consolidation
      AND/OR
   b. Minor simple effusion
3) High:
   a. Findings compatible with a moderate to large consolidation
      AND/OR
   b. Complications (e.g., significant effusions, cavities, abscess)

Exact guidance on image findings that lead to the classifications above will be based on expert consensus.

Using the above classifications, the LUS findings will be integrated into routine care guidelines as follows:

Table 1 Summary of the IMCI-PLUS algorithm



** Definitions as per WHO IMCI, South African/Tanzanian/Senegalese Standard Treatment Guidelines, except:*

- *HIV exposed, and HIV positive patients older than 12months controlled on treatment, will not be classified as severe/very severe (if not meeting other criteria for severe disease).*

*** Please note, the class and dose of antibiotic prescribed will be decided by the treating health care in line with local guidelines.*

<u>For admitted patients:</u>

Those in the intervention group with clinical deterioration will have a repeat LUS performed to assess for new evidence of consolidation in patients without antibiotics and to assess for additional/severe complications in those on antibiotics. Guidance will be provided for the interpretation of the findings in line with Table 1 above. Those with "poor response" to 1st line therapy at 72hours (lack of improvement of respiratory distress, persistence of fever >38ºC) will have a repeat LUS performed and interpretations & guidance on management of complications provided in line with Table 1 above.

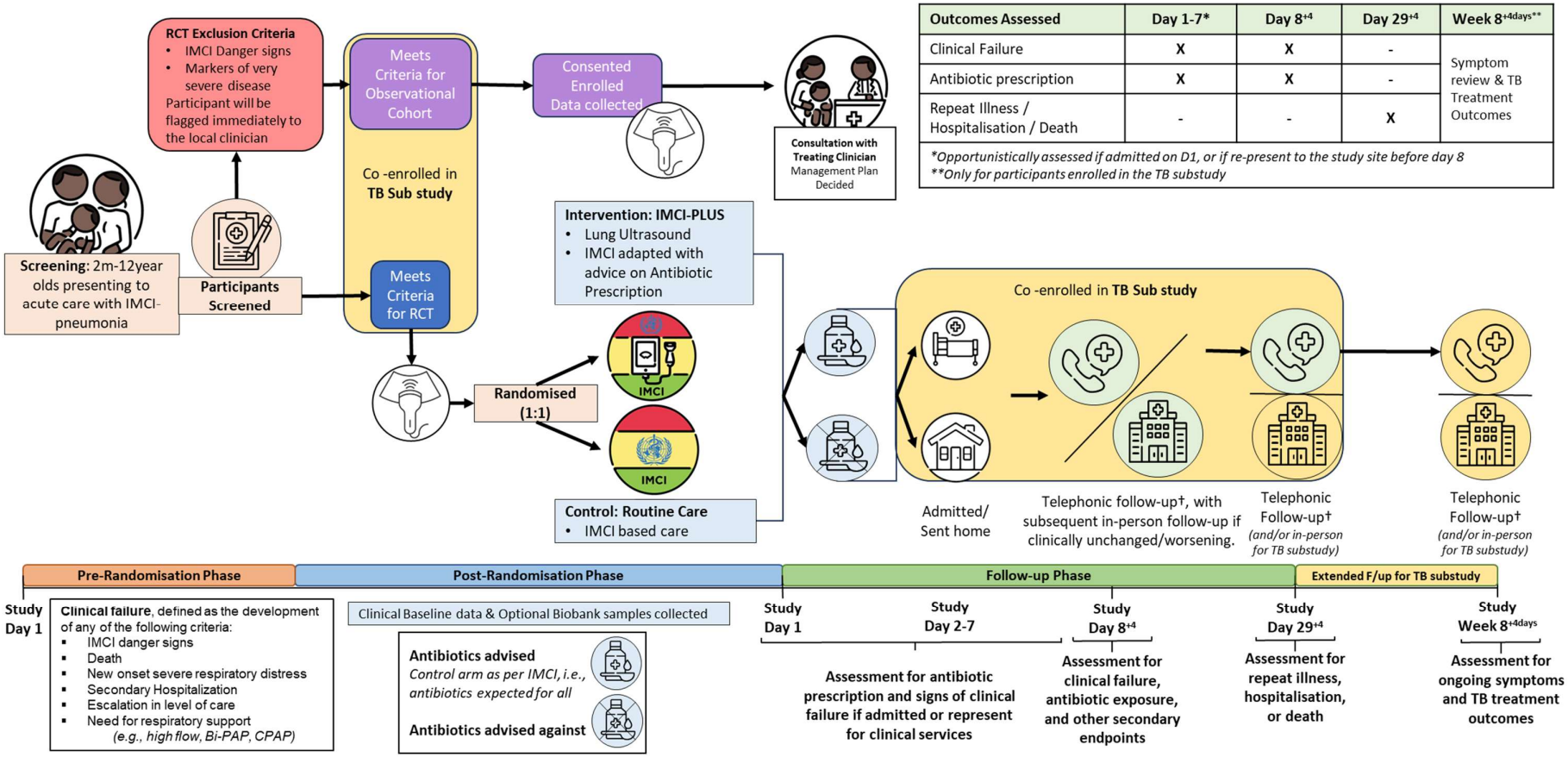
<u>For non-admitted patients:</u>

All participants will be advised to re-present to the healthcare facility (i.e., the study site) for repeat review as per the IMCI framework in the case of clinical deterioration or persistence of symptoms >3 days. If an in-person visit on approximately Day 3 is standard-of-care at the site for children with IMCI-pneumonia, then this visit will be conducted at the study site by the

research team. Transport costs will be re-imbursed to ensure access to care for families in case of clinical deterioration. Those in the intervention group with clinical deterioration will have a repeat LUS performed to assess for new evidence of consolidation in patients without antibiotics and to assess for additional/severe complications in those on antibiotics. Guidance will be provided for the interpretation of the findings in line with Table 1 above.

4.3.2 Control Group: Management based on routine care

The control group will be managed by the treating clinician as per routine care. Routine care in South African, Tanzanian, and Senegalese District/Regional Hospitals are as per the Standard Treatment Guidelines[56] which is based on IMCI for children up to 5 years of age. For older children these guidelines are based on national recommendations (see last column in Table 1). These guidelines recommend antibiotic prescriptions for all cases. In South Africa, despite slight local differences between provinces, recommended investigations include a chest X-ray and a blood culture for those classified as having “Very Severe Pneumonia”. No other investigations are advised for any other group. In Tanzania, recommended investigations include a full blood count, arterial blood gas, C-reactive protein, and chest X-ray, depending on availability[57]. The same follow-up instructions (return in case of clinical deterioration or persistence of symptoms >3 days) will be given to non-admitted patients. If an in-person visit on approximately Day 3 is standard-of-care at the site for children with IMCI-pneumonia, then this visit will be conducted at the study site. Refresher training on current local treatment guidelines will be provided prior to the start of the study. See Figure 2 for basic overview of study flow.



Outcomes Assessed	Day 1-7*	Day 8+4	Day 29+4	Week 8+4days**
Clinical Failure	X	X	-	Symptom review & TB Treatment Outcomes
Antibiotic prescription	X	X	-	
Repeat Illness / Hospitalisation / Death	-	-	X	

*Opportunistically assessed if admitted on D1, or if re-present to the study site before day 8
**Only for participants enrolled in the TB substudy

Figure 2 Flow Diagram of Study Procedures

† If uncontactable, alternate strategies such as home-visits will be considered

4.4 Study design

This is a prospective, open label, individually randomised controlled trial (RCT) with two arms (intervention and control) investigating Lung Ultrasound (LUS) as a novel tool for the management of WHO clinical pneumonia in outpatient and emergency room settings. It is a superiority trial in terms of reduction of antibiotic prescriptions and a non-inferiority trial in terms of clinical outcomes.

Advantages/ Feasibility:
An individualised RCT was chosen as it would be logistically simpler, suit the study settings, and have increased power. A cluster randomisation trial at the level of the facility would not be possible with the low number of participating sites and, at the level of the healthcare worker, due to 1) a large variation in clinical skill levels, 2) low staff numbers (with a mix of very junior and senior clinicians), and 3) frequent rotation of clinical staff between departments. These factors would result in large inter-cluster correlation coefficients and challenges around study implementation.

Methods of minimising bias
Randomisation
Participants will be randomised 1:1 to intervention and control. Participants will be randomized using block randomization with varying block sizes, stratified by site and age groups (<5, ≥5-<13), based on randomization lists generated by an independent statistician and uploaded into the study database. If internet connectivity is of concern at the site, offline randomization will be used.

Blinding
Study site blinding is not feasible in this trial and therefore it will be an open-label study. Hospital clinicians will not be able to perform LUS or receive the LUS findings for the control group as the use of LUS is not standard practice for routine management in the site hospitals. Only study staff will be conducting LUS and clinicians will be requested not to use LUS during the study.

Standardisation of assessment and management between both groups will be achieved through the creation of standardised patient assessment forms (e.g., with triage vitals, WHO pneumonia criteria, and LUS findings, interpretation, and guidance (if appropriate)) and refresher training on local treatment guidelines provided to hospital clinicians and nurses who will be treating pneumonia cases in both groups of the study.

Due to the open-label nature of the design, there is a minor risk of cross contamination. Clinicians seeing participants with negative LUS findings doing well without antibiotics may begin to change their practice with participants in the control group – assuming in cases with minor symptoms that it may be viral and not require antibiotics (despite not having LUS findings available). This potential decrease in antibiotic prescription in the control group may decrease the overall measured impact of the intervention.

Study personnel assessing the endpoints during follow-up will be blinded to the allocation to the best extent possible.

Clinical discretion and potential impact on study outcomes:
Enrolled participants may be subject to additional tests as per routine hospital practice such as inflammatory markers and CXR. Relying on these additional tests, together with clinical judgement, may influence antibiotic prescribing decisions within the intervention group, with clinicians occasionally overruling the “no antibiotic” recommendation. Such decisions reflect appropriate clinical discretion by the clinical team and are not considered protocol deviations but

reasons for non-adherence to the study recommendations will be recorded. This could be mitigated through baseline training on the role and interpretation of inflammatory markers and CXRs as well as the presentation of current data to support the diagnostic potential of LUS for paediatric pneumonia.

5 STUDY POPULATION AND STUDY PROCEDURES

5.1 Inclusion and exclusion criteria, justification of study population

Children eligible for this study will be those presenting to participating sites with an acute onset respiratory illness.
South African sites will include: Two hospitals (District or Regional) in the Ehlanzeni District, the largest of 3 districts that make up the Mpumalanga Province as well as Khayelitsha Hospital in the Western Cape Province in South Africa. If accrual is slower than anticipated at these sites, then surrounding health care facilities (hospitals and/or clinics) in Mpumalanga and the Western Cape may be added as enrolling sites. Inclusion of these sites will be subject to local institutional approval. These hospitals will be selected based on expected paediatric case load, suitability of the infrastructure for the research question (i.e. an active emergency room and/or Paediatric OPD), and the presence of an identifiable team of clinicians allocated to paediatric care. The Ehlanzeni district includes a rural population undergoing a complex and rapid health and demographic transition underpinned by the well-described South African quadruple burden of disease - continuing high levels of HIV and TB, increasing levels of non-communicable disease, and persisting high levels of maternal and child ill-health and injury. Khayelitsha is equally known to be a densely populated urban environment with a high HIV and TB burden. Malaria, however present to a low degree in Ehlanzeni, is virtually absent in Khayelitsha barring traveller's malaria. These districts are representative of other urban and rural areas in South Africa and many other LMIC regions in terms of socio-economic status, with a high burden of infectious diseases.
Tanzanian sites will include: 4-5 dispensary/health centres or hospitals in the Dar es Salaam Region serving primary/secondary care. Sites will be chosen to represent the urban/peri-urban area of Dar es Salaam with a low malaria risk/prevalence, low TB, and low HIV prevalence. Sites will be chosen based on number of children seen with LRTI and staffing (clinical officer/assistant medical officer or general medical doctor) in coordination with the district and regional offices.
Senegal Sites will include: Primary care clinics and District hospitals in Dakar, Senegal will be included. Sites will be chosen to represent the urban area of Dakar with a moderate malaria risk/prevalence, low TB, and low HIV prevalence. Sites will be chosen based on the number of children seen with LRTI and staffing in coordination with the district and regional offices.

Inclusion Criteria:
Children aged ≥60 days - <13 years presenting for acute care to a study site with WHO IMCI clinical pneumonia, defined as:

1. Cough OR Difficulty Breathing **AND**,
2. One of the below:
   2a. Fast breathing (tachypnoea)
   - > 50/minute (≥60 days–<1 year)
   - > 40/minute (≥1–<5 years)
   - > 25/minute (≥5 –<13 years)

   OR
   2b. Lower chest wall indrawing

Exclusion Criteria:
1. Presenting for repeat visit/follow-up of a treated lower respiratory tract infection (index illness / non-acute) or enrolled in the study within the preceding 28 days.
2. Currently taking antibiotic treatment for more than 48 hours at the time of enrolment
3. WHO IMCI danger signs (*inability to drink/breastfeed, vomiting everything, convulsions with this illness, lethargy/unconscious*)
4. Presence of jaundice

5. Hypoxaemia with SpO2<88%
6. SpO2<90% (*or country-specific / altitude-adjusted thresholds*):
   - With signs of severe respiratory distress (*such as nasal flaring, grunting, etc.*)
     OR
   - In children < 6 months
7. Requiring non-invasive ventilatory support (*i.e., high-flow, bi-PAP, CPAP*)
8. Underlying disease associated with increased risk of severe pneumonia or pneumonia of unusual aetiology *(e.g., WHO acute malnutrition requiring antibiotics as per local guidelines, severe immunodeficiency*)
9. HIV positive participant that is either:
   - less than 12 months old,
     OR
   - requiring admission for this illness,
     OR
   - known to be uncontrolled on treatment (with a documented VL >1000c/ml in the previous 6 months)
10. Caregiver unavailable at the time of enrolment, or unwilling, to provide informed consent

Justification:

1) Not using fever as inclusion criteria

By excluding the need for fever in the inclusion criteria it may result in the inclusion of "coughs & colds" and thus a lower pre-test probability for requiring antibiotics (less likely bacterial precipitant). We feel this is however acceptable as it increases the study's generalisability (adopting a WHO IMCI definition of pneumonia) and removes the unreliability of a "history of fever", something commonly misreported in this context

2) Exclusion of participants with hypoxaemia and severe respiratory distress or exclusion of participants under 6months of age with hypoxaemia

A child with bronchiolitis (a viral infection) can have hypoxaemia but still have a clear LUS/CXR and not benefit from antibiotic therapy. A child with a bacterial pneumonia significant enough to cause marked hypoxaemia would however have marked abnormalities on LUS/CXR. We therefore believe the inclusion of children with mild hypoxaemia is a group of significant interest that would benefit greatly from the intervention. Children < 6months with hypoxaemia are excluded from the study as a higher risk group.

3) Inclusion of HIV positive children

IMCI and local guidelines classify all pneumonias as severe if the patient is HIV positive, however patients with HIV controlled on treatment (based on HIV viral load criteria) constitute a much lower risk group compared to those with other high-risk features. We therefore aim to include them as long as they do not have additional risk factors (such as those younger than 12months old, or admitted due to the severity of the presenting illness etc.)

4) Prior exposure to antibiotics

There is a high likelihood that patients presenting via a more peripheral clinic would have received a STAT intramuscular (IM) or oral antibiotic dose. As a short course (<48hrs) is unlikely to significantly affect LUS features and interpretation, it is unlikely these patients would be misclassified by the intervention and so will be included, and the dose/duration/type of antibiotic recorded. Short course therapy of 3 days or longer has been shown to be mostly effective in some settings and hence these children will be excluded.

Children meeting all inclusion criteria, but meeting exclusion criteria 1-9, will be enrolled in an observational component of the study and in the TB substudy (See section 5.5 and 5.6).

5.2 Recruitment, screening and informed consent procedure

All paediatric patients (≥60 days – <13 years) presenting to the ER or Outpatients Department (OPD) in participating study sites will be triaged as per routine care. Study staff will screen all presenting patients during study operating hours and consecutive patient recruitment will be done for those meeting all inclusion criteria. Those showing signs of severe disease or WHO IMCI Danger signs on triage (and hence meeting exclusion criteria for the RCT) will be referred immediately to the treating clinicians as per local policy. (See Figure 2)

For those meeting inclusion criteria, sufficient time to read the informed consent form (See cover page for versions) and make an informed decision will be given to the patients/parents/caregivers before inclusion in the study. Information covered will include the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant and their parents/caregivers will be informed that the participation in the study is voluntary and that they may withdraw from the study at any time and that withdrawal of consent will not affect their subsequent medical assistance and treatment. The participants/parents/caregivers will be informed that the participants medical records may be examined by authorised individuals other than their treating clinician. In the event the participant's parent/caregiver is unable to read, a member of the study team will read it to them and provide an explanation of all study procedures as described in the informed consent document. A Patient Information Sheet outlining the study and the procedures will also be provided to the participants. There will be sufficient opportunities to ask questions. After this time the study staff will obtain written informed consent from the parent/caregiver of the participant. In the event the parent/caregiver is unable to write/sign, the agreement can be signed by a witness (e.g., a nurse or attending clinician not part of the study team). Assent will be obtained from children ≥7 - <13 years old by a similar process. If a child <7years old, or a participant deemed to be incapable of judgment, shows signs that they are unwilling to participate in the study, the participant will be excluded from participation. A copy of the signed informed consent and if applicable assent will be given to the parent/caregiver of the study participant. The consent and assent forms will be retained as part of the study records. Any refusals will be excluded from the study and participants will receive routine care.

All study documents requiring engagement with participants (e.g., informed consent forms and patient information sheets) will be translated into the local language (e.g., Swahili, Xitsonga/Shangaan, Sepedi, Swati, Afrikaans, Xhosa, French etc) and back translated to ensure accuracy.

There is no compensation or payment foreseen for the participating patients nor will there be costs incurred by the patient for any study related activities, such as consultation or investigation costs at the time of enrolment. Transportation costs for any study related in-person follow-up visits will however be compensated to ensure access to care for all children included into the study in case of clinical deterioration. In South Africa, this will depend on the site and will be guided by the SAHPRA "Guideline for clinical trial participant time, inconvenience and expense (tie) compensation model". A standard travel radius/catchment area will be drafted, and a standard amount set.

5.3 Study procedures

The study will aim for a maximum recruitment period of 24 months with an initial pilot phase. Each participant included will be followed up for a total of 28 days after enrolment (See Figure 2). Those in the TB substudy will be follow-up for a total of 8 weeks from the point of enrolment into the substudy.

The intervention is described under Section 4.3. Bias and methods to minimize bias are described under Section 4.4.

5.3.1 Data collection

Clinical, diagnostic and management data, including screening, planned and unplanned study visits, will be collected and recorded in an eCRF (e.g., REDCap®). For ease of later reference and any repeat presentation to the study site, participants' hospital folders/health cards will be marked with a study logo/marker. Study staff will receive training to standardize data collection (baseline characteristics, diagnostic test results, and outcomes).

All consented participants will have the following data collected:

Clinical Baseline Data:

This information will be collected by study staff and entered directly into the eCRF.

- Demographic and socio-economic characteristics (including age, sex)
- Relevant medical history such as:
    - Routine Healthcare card/booklet data
        - Past medical and birth history
        - Documentation of growth pattern
        - Immunisation, de-worming and Vitamin A prophylaxis history
    - HIV status / Past TB history
    - Current medications
    - Visit to a traditional healer for the current illness
    - Epidemiological exposure including
        - TB contact in the last 12 months Other sick contacts
- Specific pulmonary TB symptoms (from the WHO[1] and local TB checklists[2])
- Documentation of whether Tuberculin Skin Test was done (and results, if available)
- Other notable symptoms & clinical signs relevant to current presentation (with duration, onset, and severity where applicable)
- Vital signs and anthropometric measurements: Weight, height/length, heart rate, respiratory rate, temperature, oxygen saturation, middle upper arm circumference.
- Documentation of date of CXR, if done, and digital archiving of CXR images

At the time of enrolment and as per local guidelines, the results of tests as part of routine care will be collected, such as Malaria RDT, POC Haemoglobin, and HIV screening.

IMCI-PLUS Data:

- LUS is minimally invasive, contains no ionising radiation and poses no risk to the participants. The LUS will be performed by trained study staff.
- LAusc will be performed by trained study staff as detailed in Section 5.3.3).

Assessment of outcomes:

Outcomes will be assessed through review of their available clinical records (paper record or electronic health record) and standardised patient assessment forms from the study site. For inpatients, daily record review will be conducted along with a D8 follow-up (See Section 5.3.2 below). For outpatients, treatment will be reviewed at enrolment, at unplanned follow-up visits (in person), and at D8 follow-up (see Figure 2, Table 2). The assessments will include:

- Antibiotic-related assessment
    - Data on antibiotic prescription, duration, type, dosage, and route of administration.
- Event-related data
    - Clinical failure.

Secondary outcomes:

[1] WHO operational Handbook on Tuberculosis: Module 5: Cough longer than 2 weeks, Fever longer than 2 weeks, Lethargy, Weight loss, Haemoptysis, Night sweats, Swollen lymph nodes, Tachycardia, Tachypnoea

[2] E.g., National TB Management Guidelines – 2014 (p.114): Cough lasting longer than two weeks (if HIV+, then of any duration), unexplained weight loss, night sweats or a fever, and loss of appetite.

For assessment of secondary outcomes, key clinical and management data at enrolment, during inpatient admission, as well as D8 follow-up will be captured by research staff, including:

- Clinician derived key examination findings (including clinician interpretation of CXR or other imaging, if done and documented)
- Initial working diagnosis made by the treating clinician (e.g., IMCI classification) and/or differential diagnoses
- Management plans at enrolment and unplanned follow-up visits
    - Other investigations requested and their results (e.g., from Blood, Sputum, X-rays etc)
    - Treatment (antibiotics and other)
    - Discharge from OPD/ER or admission
    - Deviation vs conformity to the IMCI-PLUS algorithm advice or to the expected routine care (based on local guidelines)
    - Documentation of whether TB treatment or TB preventive therapy is started
- If admitted:
    - Length of admission
    - Treatments received during the course of admission and on discharge
    - Investigation results (e.g., Chest X-ray, Blood, Sputum, Urine etc)
    - Details relating to any escalation of care
    - Final hospital diagnosis
    - Final hospital outcome (Referral/transfer, discharge, demise)
- All those meeting clinical failure at D8 or with recurrent/persistent symptoms at D29 will be enrolled, with informed consent, into the TB substudy, which includes an additional 8-week follow-up period, and will be linked to routine care as appropriate.

5.3.2 Follow-up of participants

Details of Day 8 follow-up strategy:
On D8, a telephone follow-up will be conducted with the caregiver to assess for current health status, evidence of clinical failure, clinical course since enrolment, and antibiotic use. If caregivers cannot be reached by phone, other strategies will be implemented to reach these caregivers, including home visits, and establishing contact through community stakeholders (community leaders, community health workers). See Figure 3 below for a more detailed algorithm. Based on responses, participants may be flagged for in-person review and advised to return to their health facility/study site for clinical review. Participants will be compensated for transport related costs relating to this repeat visit.

Returning participants will be triaged as per routine outpatient presentation and study staff will assist in screening them for signs of clinical failure. If the participant meets WHO danger sign criteria / signs of severe disease, they will be immediately referred to a hospital clinician. A repeat LUS will be performed for all returning patients with persistent symptoms on D8 and these children will also be enrolled, with informed consent, into the TB substudy.

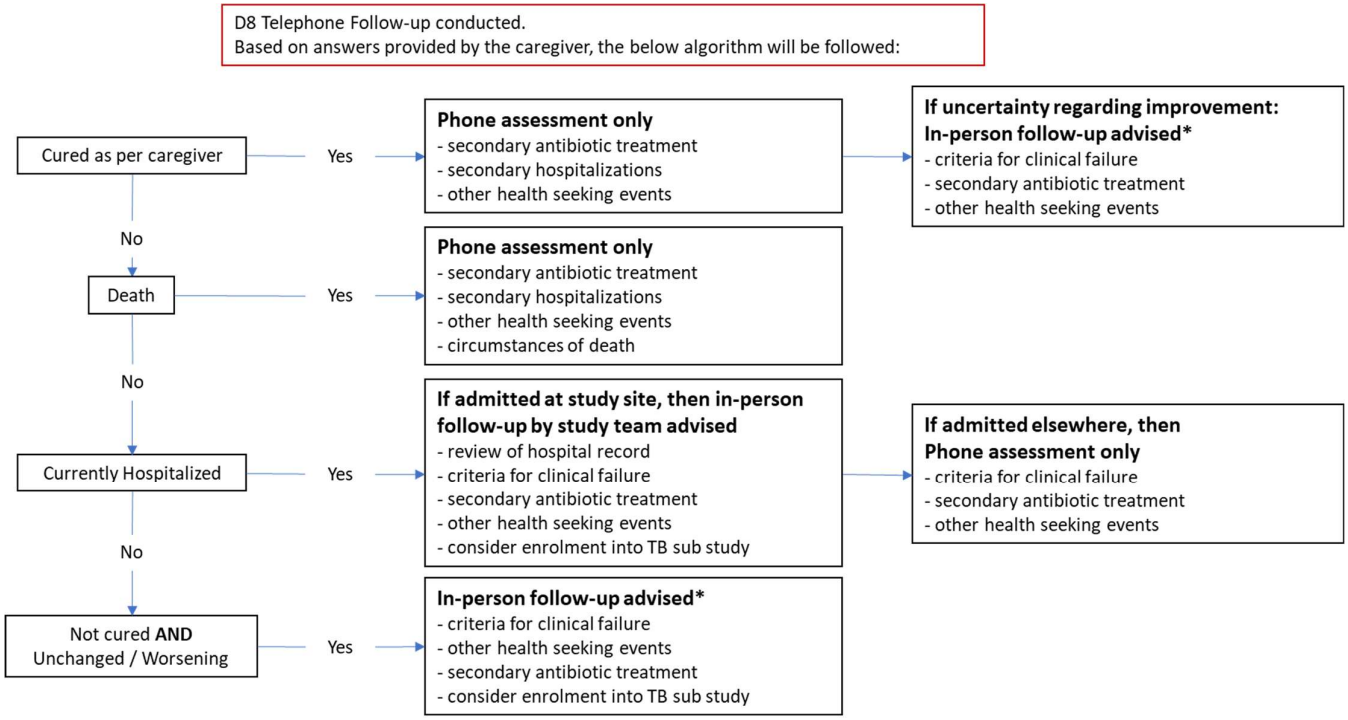


Figure 3 Schematic Presentation of Day 8 Follow-up

**Compensation for transportation to the healthcare facility will be reimbursed accordingly*
Note: If caregivers cannot be reached by phone, other strategies will be implemented (such as home visits or establishing contact through community stakeholders)

Unscheduled in-person follow-up before D8:
Participants will be managed as per the D8 in-person visit outlined above and as per standard guidelines. However, as per the intervention strategy in Section 4.3, those in the intervention group with clinical deterioration will have a repeat LUS performed to assess for new evidence of consolidation in patients without antibiotics and to assess for additional/severe complications in those on antibiotics. These children will also be enrolled, with informed consent, on the TB substudy. Guidance will be provided for the interpretation of the findings in line with Table 1 above.

Day 29-follow-up
Will be performed telephonically to assess for repeat health seeking events for a respiratory illness, hospitalisation, history of TB exposure and/or starting TB treatment, and death. All children with persistent or recurrent respiratory illness at D29, as well as those reporting TB exposure or starting TB treatment in routine care, will be reviewed in-person and enrolled, with informed consent, into the TB substudy (see Section 5.6).

5.3.3 Exploratory Outcomes and additional Investigations

LUS performed in the control group:
The control group will have LUS images collected at all in-person engagements where possible but not interpreted at the time of enrolment and as such, findings will not affect the initial or ongoing management of the participants. This data will be collected for retrospective review to better understand and characterise the control groups outcomes and to improve risk stratification for pneumonia.
All participants enrolled in the study will meet WHO clinical pneumonia definitions and as such will require antibiotics according to local standard treatment guidelines in the routine care group (control group). As the purpose of the intervention is primarily to use LUS to reduce antibiotics, the negative LUS findings are used to motivate for restrictive use of antibiotics in cases where

antibiotics are indicated. Therefore, any potentially abnormal findings in the LUS of the control group not relayed to the health care worker will not have indirect negative effects on patient management and we feel LUS is therefore justified in being collected.

In some circumstances, disclosure of LUS findings in the control group may be warranted if features are identified that are suggestive of complications of pneumonia or other significant non-pneumonia pathology requiring care beyond standard IMCI management. Such features may include evidence of empyema or loculated effusion, pneumothorax or cavity, or an abnormal mass or suspected tumour. The interpretation of these findings will be at the discretion of the study clinician and may be limited by their skill and experience beyond the study's LUS training. In these instances, the site coordinator will be informed, and disclosure of LUS findings will be documented on the protocol deviation form.

The benefit of integrating LUS findings into the management of pneumonia is yet to be determined and is the focal point of this study. Hence these LUS findings will not be integrated into routine care in the control group.

Lung Auscultation (LAusc)

LAusc sounds will be recorded from all participants using a digital stethoscope (in both the intervention and control groups) pre-randomisation. These sounds will be captured by study staff and will not be interpreted at the point of enrolment. The sounds will be recorded for 10-15 seconds in each of the 4 predefined locations as illustrated in Figure 4 (2 anterior and 2 posterior quadrants = an estimated total procedure time of 1-2 minutes)

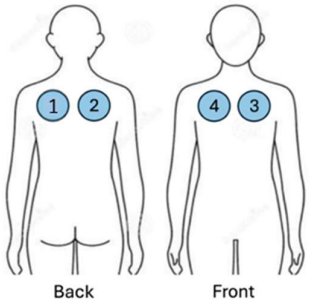


Figure 4 Lung Auscultation Sites

5.3.4 Sample Collection and Storage for retrospective testing

Subject to a separate consent form, and depending on site feasibility and participant consent, one or more of the samples will be collected for storage and retrospective testing. These samples may include:

- Nasopharyngeal swab sample (Flock swab in UTM tube)
- Saliva sample
- Maximum 1mL blood sample

We will use topical anaesthetic cream and distraction techniques where possible to minimise distress. Where a participant will require blood sample collection for their routine care, and where appropriate, the collection of the study samples will coincide with this to minimize the number of blood draws required.

Samples collected for retrospective testing (i.e., within the scope of this study and its secondary and exploratory objectives but with results not being available in real-time to inform participant management) will be temporarily stored and analysed for microbiological investigations (e.g., respiratory viral panel, SARS-CoV-2 genotyping, TB specific molecular and microbiological assays, and HIV testing where results are not already available, and other assays for infective organisms), as well as inflammatory biomarkers (CRP, PCT), and TB related mRNA

transcriptional signatures.

Residual or leftover specimens, where consent for future use ("biobanking") has been provided, may be retained in the study biobank for ethically approved future research. No host genetic analysis will be performed, and no additional or future testing outside the approved study scope will occur without new approval from the relevant Human Research Ethics Committee (HREC).

The study biobank will be developed according to the International Society for Biological and Environmental Repositories (ISBER) best practice recommendations.

In South Africa, laboratory analysis will be done in cooperation with the National Institute of Communicable Diseases (NICD) in Gauteng, South Africa.

Samples from South African sites will be biobanked at an accredited biobanking facility in South Africa such as the Sydney Brenner Institute for Molecular Bioscience (SBIMB) Biobank, South Africa, 9 Jubilee Rd, Parktown, Johannesburg, 2193, South Africa (BEC20200401) (M200469), or the Biomedical Research Unit at Stellenbosch University, Francie van Zyl Drive, Parow, Cape Town, South Africa. As for biobanking in Tanzania, samples will be stored at the MUHAS biobanking facilities.

Table 2 Overview of Study Procedure Timeline

Time since enrolment (days)	**D1**	**D1**	**D2-7***	**D8**	**D29**	**Week 8**
Visit	*Enrolment*	*Clinical Visit*	*Unscheduled in-person Follow-up*	*1st Follow-up (telephone/ in-person)*	*2nd Follow-up (telephone/ in-person)*	*3rd Follow-up (telephone/ in-person)*
Windows				+4days	+4 days	+4days
Enrolment						
Eligibility screening	+					
Informed consent	+					
Demographic data collection	+					
Baseline clinical data collection	+					
LUS	+		+**	+^	+^	+^
LAusc	+					
Randomisation	+					
Sample collection		+	+^^	+^^	+^^	+^^
Interventions						
Control group: Routine care		+	+			
Intervention group: IMCI-PLUS algorithm and guidance for clinical deterioration & persistence of symptoms		+	+			
Assessments						
Antibiotic-related assessment		+	+	+		
Event-related data (Clinical Failure)			+	+	+	
Clinical signs	+	+	+	+^	+^	+^
Clinical management		+	+	+^	+^	+^
Survival			+	+	+	+
Adverse Events		+	+	+		
TB substudy only – Symptoms and TB exposure and/or treatment history				+	+	+

For more detail regarding data points collected for Primary and Secondary outcomes, see Section 5.3.1

* *D2-7 refers to unplanned follow-up as a result of participants representing to the study site for the index illness AND/OR scheduled study visit for those sites where follow-up is routine care*

** *LUS performed at D2-7 follow-up visit if participant is:*

- *in the intervention group and clinically unchanged/ worsened and*
- *in the control group where possible/feasible*

^ *Only collected if in-person follow-up*

^^ *Sample collection after the D1 visit for the TB substudy only, inline with details in Section 5.6*

5.4 Withdrawal and discontinuation

An individual patient may discontinue their participation in the study at any point in time (i.e., refusing further data collection or follow-up) by informing their treating clinician or the study team. At this time, they will be specifically asked whether the data/samples already collected may still be used. If consent to use the data is revoked, the records and samples will be handled as outlined in Section 9.3. Anonymity is guaranteed through the process of data coding (as described in Section 9.3).
For the follow-up phone calls, the participant's primary caregiver will be asked to provide the contact of a next-of-kin in the unfortunate event of unavailability, death, or incapacitation.

5.5 Inclusion into Observational Cohort Study

Patients screened at the facility who meet all inclusion criteria but also meet any exclusion criteria numbers 1-9 (and will therefore be excluded from the RCT), will instead be recruited into an observational cohort study to obtain a more detailed understanding of all children presenting with IMCI pneumonia (see Section 5.1).
These participants will be consented on a separate consent & assent form as and receive a separate patient information sheet. All above procedures will apply (including data collection, LUS and LAusc collection, sample collection request, clinical outcomes assessment on D1, and clinical data related to any admission). Participants will have LUS collected at all in-person engagements but not interpreted at the time of the visit. Participants will however **not** be randomised and will not receive the study intervention. Participants will also receive a D8 and D29 telephone follow-up.

5.6 Inclusion in the TB substudy

The following patients will be eligible for enrolment in the TB substudy with some variation in implementation of these inclusion criteria expected between institutions. Site-specific details and procedures will be clearly outlined in each site's Manual of Operations:

- Children in the Observational Cohort Study (Section 5.5)
- Children in the RCT:
    - <2 years old, living with HIV, and/or have a recent TB exposure at D1
    - with clinical failure at D8 or persistent/recurrent symptoms at or D29
    - with TB exposure or TB disease diagnosis during the study period

These children will be recruited into the TB substudy with the aim of meeting the secondary trial objectives listed under d) in Section 4.1. These children will be specifically consented either on a separate consent form or on a separate section of the observational cohort consent form depending on their point of entry into the substudy. They will not be randomised unless they are also enrolled in the main trial but they will have all procedures outlined for the main trial and the observational cohort as well as the following additional tests:

- Collection of at least 1 respiratory sample (gastric aspirates and/or induced sputum and/or nasopharyngeal aspirates) for Xpert Ultra MTB/RIF testing and liquid culture
- Urine for lateral flow lipoarabinomannan (LAM) if living with HIV and available at the site
- CXR (both anteroposterior and lateral), if done as an investigation in the routine care pathway, for real-time interpretation by routine care clinicians to facilitate appropriate clinical care and for archiving for retrospective interpretation with CAD software
- Collection of between 1.5mL and 6mL venous blood for storage and retrospective TB biomarker testing. Total blood volumes will not exceed internationally accepted paediatric safety limits[58].

All children enrolled in the TB substudy will be linked to care within the routine care setting as appropriate and all will have telephonic follow-up visits with the study team on D8 and D29 as well as an additional telephonic/in-person follow-up at week 8 (Week 8 in-person follow-up

would be at the discretion of each site based on available resources). If caregivers cannot be reached by phone at follow-up visits, other strategies will be implemented to reach these caregivers, including home visits, and establishing contact through community stakeholders (community leaders, community health workers). If there are persistent or recurrent symptoms an in-person visit will be undertaken to ensure appropriate linkage to care for re-investigation for TB. Participants will have LUS collected at all in-person engagements but not interpreted at the time of the visit. In-person visits will also take place if any sample test positive for TB or if a child is started on TB treatment in routine care (to allow the study team to evaluate for treatment response and classification according to the standard NIH TB case classifications[54]).

6 STATISTICS AND METHODOLOGY

6.1 Statistical analysis plan and sample size calculation

Statistical analysis will be performed by the trial statistician using R or Stata. Analyses will follow CONSORT guidelines [59,60] and intention-to-treat (ITT) principles. A flowchart will describe the inclusion and follow-up of participants by study arm. Baseline characteristics will be described by study group with summary statistics such as median and interquartile range or number and percentage; no formal testing between groups will be performed [61]. Outcomes will be described by group using summary statistics. The first primary outcome, the proportion of children receiving antibiotics on D1, will be assessed for superiority on both the ITT and per protocol sets using a logistic regression model, reporting odds ratios and a modified Poisson regression reporting risk ratios and risk differences and their respective 95% confidence intervals (CI). The second primary outcome, the proportion of children with clinical failure by D8, will be evaluated using a CI approach. A figure illustrating the CIs of the risk difference and the non-inferiority margin will be presented. Primary analyses for the non-inferiority comparison will be performed on both the ITT and per protocol sets [62]. If clinical failure in the intervention group is found to be non-inferior to the control, then we will assess for superiority using the ITT set. All models will be adjusted for the stratification factors of site and age group [63].

Binary secondary outcomes with sufficient events will be evaluated in the same way as the primary superiority outcome. Rare outcomes such as death will be compared across arms using non-parametric or small sample tests. The secondary outcomes of duration of hospitalization will be tested non-parametrically using a Wilcoxon rank-sum test.

Further details will be provided in the statistical analysis plan, including approaches for the primary outcomes analysis under the estimands framework[64].

Sample Size

With an assumed baseline proportion of clinical failure in the control group of 5% and using an acceptable clinical difference of 1.5x as a non-inferiority margin (therefore a delta of 2.5%) [1–5], the estimated sample size required across all sites would be 2730 (power 85%). This would equate to 1365 participants per group for the co-primary endpoints. We however aim to enrol a total of 3000 participants under the age of 5 years of age (power >85%) as this is the age group of greatest interest based on the current IMCI framework. However, due to limited data on paediatric pneumonia outcomes in the ≥5-<13years age group we wish to include these children as well. Considering approximately 90% of children presenting for acute respiratory care in the age group ≥60 days-<13 years are <5years, we would aim for a total sample size of 3500 participants, 1750 participants per group, to account for repeat visits of the same child within the enrolment period as well as potential differences in clinical failure rates between sites. We will conduct an interim analysis assessing, among other things, LTFU and clinical failure rates. This will be done approximately 25% through the RCT and the sample size adjusted accordingly if appropriate. The planned breakdown of participant enrolment per country is as follows: Tanzania – 2000 participants, Senegal – 500 participants, South Africa – 1000 participants. As

the expected difference in antibiotic prescription rates is expected to be large, this sample size will provide sufficient power to test for a clinically meaningful difference of 20% on Day 1 and 15% by Day 8 (secondary outcome).

6.2 Handling of missing data and drop-outs

Missing baseline and outcome data will be summarized by study group. Multiple imputation approach under the assumption of data missing at random will be used to account for missing outcome data. Details will be provided in the statistical analysis plan.

6.3 Economic Evaluation

We will conduct a multi-national economic evaluation of integrating the Lung Ultrasound (LUS) into current IMCI based management guidelines for pneumonia for Senegal, South Africa and Tanzania. We will conduct a cost effectiveness analysis, using natural units informed by the trial outcome such as a percentage reduction in antibiotic prescribing rate and a cost utility study using Disability Adjusted Years (DALYs) as a measure of health outcome. Our study comparators are current IMCI based management for pneumonia for each country (current practice) versus current IMCI based management for pneumonia for each country plus LUS (IMCI-PLUS algorithm).

We anticipate that the heterogeneity in resource use and costs across the three countries is potentially substantial given their differing health systems therefore, study perspective will not be uniform across countries. Public primary healthcare in South Africa is largely free to the patient and almost all costs are borne by the government therefore the economic evaluation will be done from the government's perspective. Patients in Senegal and Tanzania bear a significant portion of healthcare costs when accessing public primary care services so the analysis in these two countries will be done from a societal perspective.

The target population for the analysis are children aged ≥60 days-<13 years with WHO IMCI clinical pneumonia. Specifications of the target population including exclusion and inclusion criteria are described elsewhere in the protocol. The time horizon for the analysis is equivalent to the treatment duration of a pneumonia episode, including a possible second-line treatment.

We will perform the economic evaluation of using an excel decision analytic model (Figure 5). We will conduct a split analysis using a multi country costing approach. We assume that clinical effects are homogenous across the three countries but not costs. We will apply unit cost estimates from individual countries to counts of resource use in each of those countries. Costs

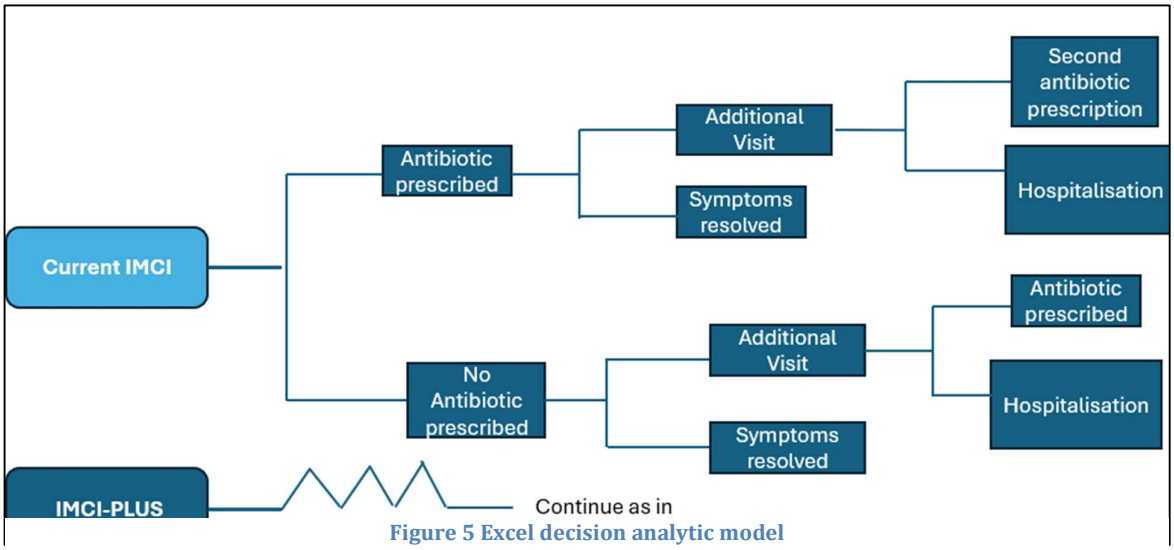


Figure 5 Excel decision analytic model

of health care and illness will be estimated at individual patient level, including costs to health services and patient participants of health care utilisation such as primary care visits, specialist referrals, emergency care visits, hospital admissions, user fees.

Identification and quantification of resources used by each participant during the trial will be extracted from patient notes, electronic medical records, patient administration systems and a trial specific form. Unit cost of resources provided by the government will be obtained from respective government documents and market prices will be used for out-of-pocket payments incurred by patients. Monetary values will be expressed in each country's respective currencies, i.e. South African Rand, Franc of West Africa for Senegal and Tanzanian Shilling and the United States Dollar. There will be no discounting as the time horizon is less than a year.

Using the average costs and outcomes for each alternative (i.e., for each arm in the trial), the two alternatives will be compared to calculate the incremental costs and compare them to the incremental effectiveness outcomes. The results will be expressed as an Incremental cost effectiveness ratio (ICER) which is a measure of the additional cost per unit increase of benefit in the primary outcome (reduction of antibiotic prescriptions). The following formula represents the calculation of the incremental cost-effectiveness ratio (ICER):

$$ICER = \frac{Costs^{IMCI-PLUS} - Costs^{IMCI}}{Benefits^{IMCI-PLU} - Benefits^{IMCI}}$$

The results of the cost-effectiveness analysis will be compared to the South African specific threshold to determine whether the new intervention is cost-effective or not. For Senegal and Tanzania, the WHO recommended threshold will be used. Deterministic and probabilistic sensitivity analysis will be carried out to assess the degree of uncertainty in the ICER. Results will be presented on tornado diagrams, scatter plots and cost-effectiveness acceptability curves.

In addition, we will carry out a cost utility analysis, Disability Adjusted Life Years (DALYs) as outcome. DALYs will be determined by calculating years of life lived with disability and years of life lost to premature mortality based on outcome data from the trial and country specific life tables. This will estimate the incremental cost per DALYs averted and the probability of cost-effectiveness at various levels of willingness to pay for a DALY.

A budget impact assessment for the South African, Tanzanian, and Senegalese governments from the healthcare payer's perspective will be carried out for a 5-year time horizon. A model will be developed to describe the financial resources associated with the usual practice over the course of the National Department of Health's budgeting cycle (one year). This will represent the base case or 'reference case'. The comparative scenario will model the required changes in health service resourcing that are expected to result from the adoption of the IMCI-PLUS program, including indirect and downstream impacts on other parts of the health service. Resource use data will be sourced from the costing analysis. There will be no discounting of costs as a budget impact analysis aims to present the actual financial implications required to deliver the new intervention over each year of the analysis. Inflation rates will be applied to costs/prices of resources used in the model for subsequent years. All model assumptions and data inputs will be described in full. Justification for the inclusion or exclusion of relevant model parameters will be provided. We anticipate using a simple spreadsheet-based model for the analysis. Scenario sensitivity analyses will be conducted to assess the impact of varying model inputs on the affordability of the IMCI-PLUS program

7 REGULATORY ASPECTS AND SAFETY

7.1 Local regulations / Declaration of Helsinki

This study is conducted in compliance with the protocol, the current version of the Declaration of Helsinki [65], the HRA [66] as well as locally relevant legal and regulatory requirements. The study will be conducted in accordance with the principles of Good Clinical Practice (GCP) [67].

7.2 Adverse Events and notification of safety and protective measures

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical investigation subject which does not necessarily have a causal relationship with the trial procedure. An AE can therefore be any unfavourable or unintended finding, symptom, or disease temporally associated with a trial procedure, whether or not related to it.

A Serious Adverse Event (SAE) will be defined as per Swiss ClinO, Art. 63 [68,69], or equivalent South African/Tanzanian/Senegalese regulation, as any untoward medical occurrence that

- Results in death or is life-threatening,
- Requires in-patient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity

Adverse Events will be collected until D8, death will be asked at the D29 follow-up. The following symptoms are expected as part of a child with an acute infection and will not be considered as an adverse event: diarrhoea, fever for less than 7 days, cough, diminished appetite, vomiting, rash (besides severe drug related rashes such as Steven Johnsons or skin rashes related to anaphylaxis).

Both Investigator and Sponsor Representative make a causality assessment of the adverse event to the trial intervention, (see table below based on the terms given in ICH E2A guidelines [70]). Any event assessed as possibly, probably, or definitely related is classified as related to the trial intervention.

Relationship	Description
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Both Investigator and Sponsor Representative make a severity assessment of the event as mild, moderate or severe. Mild means the complication is tolerable, moderate means it interferes with daily activities and severe means it renders daily activities impossible.

Note that the initial hospitalization for children does not count as an SAE as the condition for which the child was hospitalized occurred prior to the study procedure, classifying it as a pre-

existing condition and not an AE. Any secondary hospitalization (see definition in Section 4.3) or upward referral (of initially admitted children to a referral hospital) will be reported as an SAE.

7.2.1 Reporting of SAEs

All SAEs are documented and reported immediately by the site (within a maximum of 24 hours of the investigator becoming aware of the event) to the Sponsor Representative of the study. If the SAE occurs at one of the study sites, the Principal Investigator reports the events to the Institutional Review Board/ Ethics Committee concerned as per relevant reporting requirements. If immediate safety and protective measures have to be taken during the conduct of the study, the investigator notifies the Ethics Committee of these measures, and of the circumstances necessitating them, within 7 days.

7.2.2 Follow up of Serious Adverse Events

SAEs should be followed until resolution or stabilisation. Participants with ongoing SAEs at study termination will be further followed up until recovery or until stabilisation of the disease after termination. A further SAE form, indicated as 'Follow-up', should be completed and sent to the Sponsor Representative as soon as new information becomes available.

7.3 (Periodic) safety reporting

An annual safety report (ASR) is submitted at least once a year to the Ethics Committee prepared by the Sponsor Representative through the participating Investigator (ClinO, Art. 43 Abs 1). More frequent reporting may occur if required by local regulations.

7.4 Amendments

Substantial changes to the study setup and study organization will result in submission of an amendment of the protocol and relevant study documents to the Ethics Committee for approval before implementation. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Ethics Committee (see immediate safety and protective measures). Such deviations shall be documented and reported to the Ethics Committee as soon as possible.

The ASR will be submitted once a year to the competent EC together with the ASR.

7.5 Notification and reporting upon completion, discontinuation or interruption of the study

Upon regular study completion, the Ethics Committee is notified within the timeframe specified in their standard requirements/guidelines.

The Sponsor Representative may terminate the study prematurely according to certain circumstances, e.g.

- Ethical concerns,
- Insufficient participant recruitment,
- When the safety of the participants is doubtful or at risk
- Alterations in accepted clinical practice that make the continuation of the study unwise, OR
- Early evidence of harm or benefit of the intervention

Upon premature study termination or study interruption, the Ethics Committee is notified within 15 days.

A final report is submitted to the Ethics Committee after completion or discontinuation of the study within a suitable timeframe as outlined in their standard requirements/guidelines.

7.6 Insurance

Appropriate insurance will be purchased before the start of the study.

8 FURTHER ASPECTS

8.1 Overall ethical considerations

Though LUS is increasingly used in the management of clinical pneumonia in children, its additional benefit has not been rigorously studied. This is particularly relevant in IMCI settings, where additional diagnostics must demonstrate potential clinical benefit before integration into current management guidelines is considered. The inclusion criteria were chosen based on the current IMCI framework, allowing for interpretation (including generalizability) within the IMCI framework. Randomization of participants is necessary since there is currently no diagnostic reference standard for bacterial pneumonia (e.g., a reference standard for the need for antibiotic treatment) and diagnostic accuracy studies for LUS against other reference standards (e.g., radiography or lab investigations) are of limited use.

8.2 Risk-benefit assessment

The use of LUS may lead to better targeting of children in need for antibiotic treatment. This reduction in antibiotic treatment is expected to reduce side effects for patients, long-term detrimental health effects for patients from antibiotic use (including asthma, auto-immune conditions, diabetes, obesity, and neurodevelopmental conditions), and antimicrobial resistance, which is a major global health problem. The risk of the intervention is judged as comparable to standard medical care. The proposed intervention is based on previously validated tests. The risks of this study are minimal.

A potential risk is related to a participant with bacterial pneumonia not receiving an antibiotic. However, there are several layers of safety included in the study design to mitigate this risk:

- Eligibility criteria have been carefully selected to only include children that may truly benefit from the intervention. Patients with very severe symptoms requiring close inpatient monitoring are excluded. Patients with a higher baseline risk for bacterial pneumonia (immunodeficiency, severe acute malnutrition) will be excluded.
- Systematic clinical outcome assessments and safety monitoring will be undertaken (including the establishment of an Independent Data Monitoring Committee for regular review of cumulative safety and study conduct data, see Section 2).

9 QUALITY CONTROL AND DATA PROTECTION

9.1 Quality measures

The Sponsor Representative will be responsible for implementing and maintaining quality assurance and quality control systems with written instructions to ensure that the trial is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, and the applicable regulatory requirements. The local principal investigators are responsible for proper training of all involved study personnel.

The local principal investigators (or delegated study personnel) will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject enrolled into the study.

For quality assurance the sponsor, the EC or an independent trial monitor may visit the research sites. Direct access to the source data and all study related files is granted on such occasions. All involved parties keep the participant data strictly confidential.

9.2 Data recording and source data

The electronic case report form (eCRF) will be set up by the Sponsor Representative. Individual accesses to eCRF will be given to each local investigators and delegated study personnel in order to report site-specific coded study data. Data will be entered into the eCRF (REDCap®) by the study team and validated for completeness and discrepancies automatically. An audit trail system maintains a record of initial entries and changes (reasons for changes, time and date of changes, user identification of entry and changes).

Source data must be available at each site for each participant. The source data must include the original documents relating to the study (paper or electronic records), as well as the medical treatment and medical history of the participant. Each site will define the unique source data corresponding to each eCRF entry in a study-specific “Source Data Location List” (SDLL), allowing both the local investigators and monitors to access the same source. Direct entry into the eCRF will be allowed and clearly identified in the SDLL. Identifying data for phone follow-up visits will be collected and kept locally at the site.

9.3 Confidentiality and coding

9.3.1 Data management and Coding

Applicable laws and regulations will be adhered to, including but not limited to the General Data Protection Regulations (GDPR) and Protection of Personal Information Act 4 of 2013 (POPIA), pertaining to the use, transfer, processing and storage of Data [71].

Trial and participant data will be handled with uttermost discretion and is only accessible to authorised personnel who require the data to fulfil their duties within the scope of the study. On the CRFs and other study specific documents, participant identifying data such as names and contact details will only be available to site research staff for quality control, participant follow-up, and data linking purposes, and all participant files will be securely stored. Participant number coding will be done using the Electronic Data Capture (EDC) software. Biological material in this study is not identified by participant name but by a unique participant number. Biological material is appropriately stored in a restricted area only accessible to the authorised personnel. Data management will be defined in greater detail in a data management plan that will be put in place before initiation of the first site.

9.3.2 Data security, access and back-up

The study team of a local site will only have access to the data of the participants and to the data entered in this center. The study team of a local site will access the data through a tablet computer or a computer. Access to the secured platform (REDCap®) will be password-protected. Back-ups will be performed on a regular basis.

Members of the site study coordination team will be authorized to enter and access data into the eCRF for the specific sections of which they are responsible (i.e., follow-up visits if applicable). They can access these data for all the patients included in the study. Only the study identifier will be entered into data storage applications of the portable ultrasound devices.

9.3.3 Analysis and archiving

Completion status of each section/form of the eCRF will be predefined during database development. The system will include visual aids to inform of data entry completion.

The database will be locked after study data validation activities and monitoring review have been completed. After study completion and publication of the dataset, apart from the information directly related to the site and potentially identifying information (e.g., date of consultation), data will be made accessible in an open access data repository after the main study results are published. Data will be made available to other researchers pending approval by the Sponsor Representative.

9.3.4 Electronic and central data validation

Predefined checks (validation rules) will be included to limit the occurrence of data entry mistakes.

Data will be centrally checked on a regular basis to identify missing items or discrepancies as well as low patient recruitment. In the case of data inconsistencies, electronic queries may be shared with the relevant site to resolve.

9.3.5 Retention and destruction of study data and biological material

All study data are archived for 10 years after study termination or premature termination of the study. The source data will remain in the respective hospitals and stored according to specific regulation.

The biobank, as according to best practice recommendations, ensures that participants are aware of their right to withdraw, without justification, penalty or disadvantage, the requirements for exercising that right, and the implications of and any limits to exercising that right.
The Sponsor Representative ensures that traceability of the samples and data is possible to enable participant withdrawal.
Different levels of withdrawal may apply including:

- **No further contact:** No further contact is made with the participant but previously obtained biospecimens and data are permitted to be retained and used, and further data can be obtained from health records.
- **No further access**: No further contact with the participant or access to health records is permitted but previously obtained biospecimens and data can be continued to be stored and used.
- **No further use:** No further contact would be made with the participant, and data and biospecimens would no longer be available for research. It would be necessary to destroy biospecimens, with archiving of data for audit purposes only.

Participant samples collected for biobanking will be frozen and kept anonymous (only with code) for a maximum of 10 years. The samples will be destroyed after 10 years, or before by decision of the study management. No future testing will be done beyond analyses specified in this protocol on samples without approval of the EC.

Samples from the South African sites will be stored at an accredited biobanking facility, such as: Sydney Brenner Institute for Molecular Bioscience (SBIMB) Biobank, South Africa, 9 Jubilee Rd, Parktown, Johannesburg, 2193, South Africa (BEC20200401) (M200469), or the Biomedical Research Unit at Stellenbosch University, Francie van Zyl Drive, Parow, Cape Town, South Africa. As for biobanking in Tanzania, samples will be stored at the MUHAS biobanking facilities.

10 MONITORING AND REGISTRATION

The monitoring activities will be coordinated by the Swiss TPH Clinical Operations Unit. Local research units will be contracted by Clinical Operations Unit to perform monitoring activities at local sites.

A risk-adapted monitoring strategy will be developed in accordance with relevant regulations and the monitoring strategy (nature and extent of the monitoring activities) will be described into a joint monitoring plan. In principle, site initiation visits will be conducted on each site in order to ensure that all sites are ready to start the trial. Then interim monitoring visits will be performed remotely or on site depending on the situation and focusing mainly on safety, intervention adherence, and patient eligibility. Data from participant records (source documents) will be reviewed by local monitors against data reported in the eCRF in order to check completeness, validity, consistency, and adherence to protocol specifications. Queries regarding missing, questionable or inconsistent data will be documented. Monitoring activities will be documented in a monitoring report after each monitoring visit. A (remote) closeout monitoring visit per study site will be performed at the end of the trial to ensure all pending actions are resolved and investigator site file is ready for archival.

11 FUNDING / PUBLICATION / DECLARATION OF INTEREST

The study is financed by grant PZ00P3_193342 of the Swiss National Science Foundation (Ambizione Call 2020) and by grant 101145822 of the European and Developing Countries Clinical Trials Partnership (EDCTP) The responsibility of the budget is covered completely by the Sponsor Representative. There is no other financial support.

There will be a written agreement between institutions describing the collaboration.

The data from all centres will be analysed together and published as soon as possible in peer-reviewed journals, as well as being presented at national and/or international conferences. Individual groups and clinicians must not publish data concerning their participants that are directly relevant to questions posed by the study until the study coordination group has published its report. The study coordination group will form the basis of the Writing Committee and will advise on the nature of all publications.

Then, results will be disseminated through relevant clinical and policy groups. The results of the study will also be presented in national and international conferences relevant to the field. Several publications in high-impact factor journals are expected to be produced out of this trial. Reporting of the trial will follow CONSORT 2010 guidelines for reporting and ICMJE recommendations for authorship.

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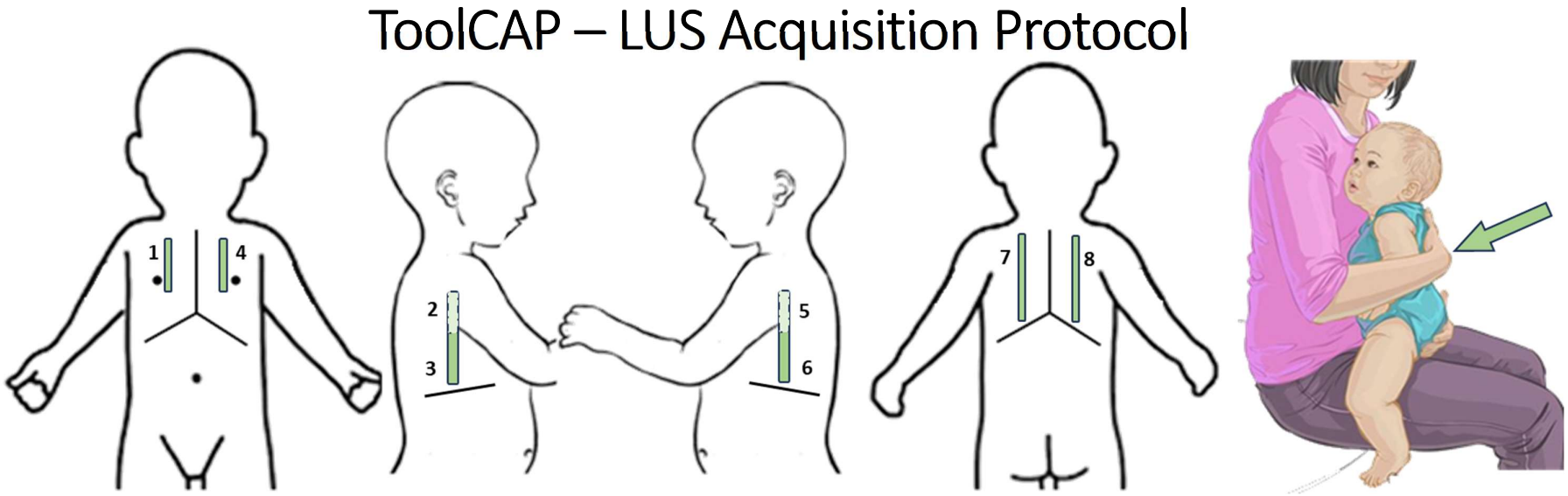
13 APPENDICES

13.1Appendix 1: Draft LUS Acquisition and Documentation Protocol



The Lung acquisition protocol is adapted from that suggested by Copetti and Cattarossi et al [72]. We opt for an 8-point "Sliding protocol", where a 10-15second video clip is recorded in sagittal orientation, sliding from the most superior region down until the diaphragm is encountered in the outlined regions. The sonographer is asked to ensure an adequate view of any pathology encountered. An additional video on each lateral region to assess for the "spine sign" is also collected – this is a static/ non-sliding video.

Right Anterior & Lateral	Left Anterior & Lateral	Posterior
1 = Right Anterior (RA) 2 = Right Lateral (RL) 3 = Right Lateral (Spine Sign)	4 = Left Anterior (LA) 5 = Left Lateral (LL) 6 = Left Lateral (Spine Sign)	7 = Left Posterior (LP) 8 = Right Posterior (RP)
IN ALL REGIONS (1,2,4,5,7,8)	**FOR LATERAL INFERIOR VIEWS (3 & 6)**	**PLEASE NOTE**
(7.5–10 MHz linear probe preferred, in older/school children, consider a 3.5–5 MHz convex probe) a. VIDEO at 5cm depth sliding from top to bottom (until diaphragm reached) b. Video should be approx. 10-15seconds maximum c. Ensure to allow good view of pathological areas	**ADD THE FOLLOWING:** VIDEO 5 sec SPINE&CURTAIN SIGN using a 3.5–5 MHz convex probe (Must include spleen/liver + kidney + diaphragm + spine + anterior lung tip/curtain)	If you see a pleural effusion in the lower views – add a view in abdominal mode/convex probe as this gives you a MUCH clearer depth of view