

**EVALUATING POINT
OF CARE
ULTRASOUND TO
IMPROVE TB
DIAGNOSIS IN
CHILDREN**

**STUDY PROTOCOL – VERSION 1.13 November
2021**

*MÉDECINS SANS
FRONTIÈRES &
MINISTRY OF
HEALTH*

Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral treatment
ATT	Antituberculosis treatment
CHW	Community health worker
CSF	Cerebral spinal fluid
CRF	Clinical report form
DST	Drug susceptibility testing
EPTB	Extrapulmonary tuberculosis
IDP	Internal displaced population
IPD	In-patient department
ITFC	Inpatient Therapeutic Feeding Centre
HIV	Human immunodeficiency virus
MSF	Médecins Sans Frontières
MoH	Ministry of Health
MTB/RIF	Mycobacterium tuberculosis / Rifampicin resistance
OCBA	Operational Centre Barcelona-Athens
OPD	Out-patient department
NICU	Neonatal intensive care unit
PICU	Paediatric Intensive Care Unit
POCUS	Point-of-care ultrasound
SAM	Severe acute malnutrition
SOP	Standard operating procedures
TB	Tuberculosis
US	Ultrasound

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1. Summary

Title	EVALUATING POINT OF CARE ULTRASOUND TO IMPROVE TB DIAGNOSIS IN CHILDREN
Design	Multicentric study (South Sudan and Guinea Bissau). Longitudinal prospective cohort study.
Rationale	<p>TB diagnosis in children is particularly challenging in low-resource and conflict-affected settings, and a high number of children remain undiagnosed and untreated. A delay in TB diagnosis can lead to an increase in preventable morbidity and mortality.</p> <p>Data from pilot studies in South Africa suggest that TB-focused POCUS improves timely diagnosis of childhood TB and is a valuable tool for monitoring treatment response while being a non-invasive and low cost bedside tool. Moreover, POCUS is widely distributed in MSF missions. The study aims to refine and adapt TB-focused POCUS protocols (i.e. FASH, Chest) for children with presumptive TB living in different TB endemic settings and with differing co-morbidities (i.e. HIV, malnutrition) and differential diagnoses (i.e. Cystic Echinococcosis).</p>
Main objectives	To describe the findings obtained by POCUS methodology for pulmonary and extra-pulmonary tuberculosis in children per TB category.
Secondary objectives	<ol style="list-style-type: none"> 1. To establish the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of POCUS positive (any of 8 pre-established sonographic signs) as a composite against a composite reference of the final diagnosis (confirmed TB, unconfirmed TB or unlikely TB) 2. To describe the sonographic signs according to HIV status (positive, negative) and to nutritional status (SAM or not SAM) 3. To determine the proportion of children with improvement or resolution of sonographic signs and the proportion without improvement of sonographic signs at 2 months of follow-up in children with and without TB 4. To describe operational aspects of POCUS: compliance with POCUS examination; quality of POCUS; duration of POCUS; mean time to definitive diagnostic in POCUS positive results compared to POCUS negative results; proportion of children who started TB treatment on basis of POCUS positive results.
Population	Children with presumptive TB in Malakal (South Sudan) and in Bissau (Guinea Bissau).
Timeframe	January 2019 to July 2021
Expected results	Identification of main POCUS determinants for TB diagnosis in children and include them in TB algorithms while adapting and simplifying the POCUS protocol to better adjust it to the local context.
Partnership	Ministry of Health in South Sudan Ministry of Health in Guinea Bissau

2. General Information

Title and date	EVALUATING POINT OF CARE ULTRASOUND TO IMPROVE TB DIAGNOSIS IN CHILDREN, March 2019
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Ministry of Health (MoH) Guinea Bissau

3. Background

a. Tuberculosis in children

Despite the increased availability of diagnostic tests as well as a curative and preventive therapy, tuberculosis (TB) remains an important cause of morbidity and mortality. TB is the main infectious disease killer in the world and remains an important burden in resource-limited settings. WHO estimates that 10.4 million people suffered from TB in 2016, of which 1.7 million people died (1). Developing countries account for more than 90% of these cases and deaths.

Tuberculosis is also a major cause of morbidity and mortality among children: in 2016, 1,000,000 children became ill from TB, of which 250,000 died -80% of them were under 5 years old (2). Childhood TB has been a largely neglected subject for organizations dedicated to TB or child health.

Active TB in children is also a serious and frequent co-infection of HIV or a co-morbidity of malnutrition in endemic environments (3-6). Malnutrition is an independent risk factor for both development of TB and mortality due to TB (7-9), and is associated with more severe forms of TB (8). It is essential to better integrate the diagnosis of tuberculosis into vertical programs for non-infectious diseases, especially for malnutrition services (5,6,10,11).

b. TB diagnosis in children

According to WHO, the TB diagnostic gap world-wide is still enormous: 39% of all patients suffering from TB remained undiagnosed in 2016 (1). This gap is even higher when it comes to paediatric TB. In some African settings, only 20% of estimated cases were diagnosed (12).

The diagnosis of tuberculosis in children is particularly difficult and is essentially based on clinical symptoms. TB scoring systems have not proven to be effective and young children have difficulty expectorating adequate samples for microbiologic investigation. Even if samples are obtained by partly invasive procedures such as naso-pharyngeal aspiration or gastric lavage, the positivity rate in smear or culture is low (13,14). Similarly, radiographs and skin tests of tuberculin give only very limited information in children and are rarely available in contexts where Médecins sans Frontières (MSF) works.

In addition, TB cultures and Xpert MTB / RIF® (Cepheid, Inc.) are often not available in endemic areas. Traditionally, TB culture has been considered as the gold standard for TB diagnosis. However, access to culture and time till final result make culture not feasible as a regular test in most of the contexts where MSF works. This is the reason why an international expert panel established that the case definition of “confirmed tuberculosis” includes a positive WHO-endorsed nucleic acid amplification test (Xpert MTB/RIF) in addition to culture confirmation using a valid respiratory specimen for microbiologic examination, irrespective of the culture result (13).

Even when there is access to TB culture or Xpert MTB/RIF, we are confronted with the challenge of getting an appropriate sample from children. Clinical signs and symptoms alone are often variable and therefore considered too inaccurate for TB screening. This is particularly true for children under 5 years old, children with HIV and for children with severe acute malnutrition. TB suggestive signs and symptoms such as cough, fever and low weight gain are also common in other childhood diseases, further complicating diagnosis (15).

It is therefore essential to continue research that may improve the diagnosis of tuberculosis in children. Timely initiation of appropriate treatment reduces morbidity and mortality. As such, there is an urgent need

for appropriate tools which allow reliable and timely diagnosis of childhood tuberculosis. Improving childhood diagnosis will also reduce over-diagnosis and over-treatment, which exposes children to unnecessary toxicity and wastes resources.

c. Use of Xpert MTB / RIF for TB diagnosis

Xpert MTB/RIF is widely used for TB diagnosis in pulmonary samples. A recent meta-analysis (16) showed that, compared with microscopy, Xpert offers better sensitivity (increased by 36-44%) for the diagnosis of pulmonary tuberculosis in children. However, its sensitivity remains suboptimal compared with culture tests (pooled sensitivity of 62-66% in respiratory samples, specificity 98%). Xpert scale-up can improve access to tuberculosis diagnostics for children. Culture remains the gold standard but, in the mentioned meta-analysis, among all samples analysed, only 12% had a culture positive.

The use of Xpert MTB/RIF has also been extended to extra-pulmonary TB forms. Recent meta-analysis and literature review (17,18,19) on the diagnostic accuracy of Xpert MTB/RIF in extra pulmonary samples, showed that Xpert sensitivity differed substantially between sample types, with higher sensitivity for lymph nodes (pooled sensitivity ranged between 87 and 96%) and CSF (pooled sensitivity ranged between 80.5 and 85%), and had a high specificity (pooled specificity between 97 and 98.7%). These findings led the WHO recommend Xpert MTB/RIF as the primary diagnosis test for lymph node and meningitis TB (20).

d. Point-of-Care Ultrasound (POCUS) for TB diagnosis

The use of POCUS has been extended into daily clinical practice throughout various medical specialties and is well acknowledged as a useful bedside diagnostic tool. POCUS is meant to be an efficient tool to reduce time to diagnosis and management decisions. Further, it is an inexpensive, safe and portable imaging tool with a special utility in resource-limited settings (21). Focused Assessment with Sonography for HIV-associated Tuberculosis (**FASH**) is the most widely studied and implemented application of POCUS in infectious diseases to date (22-28) and pulmonary POCUS is increasingly being used to diagnose pneumonia.

The value of US for diagnosing extra-pulmonary tuberculosis in adults has long been recognized. The sonographic features suggestive of extra-pulmonary tuberculosis in populations with a high prevalence of tuberculosis (and HIV co-infection) include:

- Pleural effusion, particularly when unilateral. In a study from sub-Saharan Africa, unilateral pleural effusion was caused by tuberculosis in over 90% of cases and was highly associated with HIV infection (29);
- Pericardial effusion, which is consistently reported to be due to tuberculosis and to be associated with HIV co-infection in the vast majority of cases in Africa (30). Pericardial fluid can easily be identified by POCUS (31). POCUS can additionally be used to assess hemodynamic significance of the pericardial effusion, which aids in the decision to perform a pericardiocentesis (32).
- Enlarged abdominal lymph nodes and splenic micro-abscesses have been repeatedly reported as characteristic findings of abdominal tuberculosis not only in HIV-infected patients, but also in HIV-uninfected patients (33,34,36).

Despite this evidence, the impact of POCUS on clinical decision-making for paediatric TB in low-resource settings has not yet been well studied. POCUS is especially attractive for children as a bedside and non-invasive procedure. In addition, the high proportion of extra-pulmonary TB in children can be translated into high yield US findings, which are easily recognizable with basic US training (35). POCUS can then have a role in contributing to a timely diagnosis of paediatric TB and in monitoring the treatment response (36).

However, more studies to define the characteristic ultrasound findings in different endemic settings, at different health care levels or in different co-morbidities (such as malnutrition) need to be done for an informed application of POCUS for TB in routine patient management.

The abnormal findings on FASH ultrasound exam may have various aetiologies. However, in a high-prevalence setting, certain sonographic findings can justify initiation of tuberculosis treatment as tuberculosis is the first differential diagnosis (37).

Many studies have shown the excellent performance of lung ultrasound to diagnose pneumonia (38). Few studies looking at lung POCUS performance to diagnose pulmonary TB (39,40) have shown that POCUS can be a complementary tool in evaluating patients with suspected lung TB. POCUS scanning of the mediastinum can detect mediastinal lymphadenopathy, a common manifestation of childhood tuberculosis (41). Lung and mediastinal findings suggestive of childhood TB are traditionally visualized by CXR. However, CXR is often not available or affordable in resource-limited settings (42). In addition, there is high inter-reader variability (43,44,45) and unwanted exposure to ionizing radiation. Lung ultrasound for TB appears to be a promising imaging tool in the absence of CXR or in addition to CXR. It allows clinicians to visualize features compatible with either childhood TB or pneumonia, part of the differential diagnosis for TB. Finally, it allows for monitoring treatment response in children diagnosed with TB or with pneumonia. More data on lung ultrasound in paediatric TB suspects is needed.

In regards with equipment, there are good quality low cost devices [36] which require two transducers (linear and convex) at a total approximate cost of 2.500\$. US devices have batteries available and the running costs comprise ultrasound gel (0.1\$ per exam) and maintenance. Regarding staff training, POCUS for EPTB (FASH) can be taught to clinicians efficiently in 2-day courses [32] and POCUS for pneumonia can be taught to clinicians efficiently in 1 hour training [54].

e. Differential diagnosis for childhood TB

The main differential diagnoses to be considered for children with TB suspicion are:

- Visceral Leishmaniosis (in South Sudan, not endemic in Guinea Bissau)
- HIV (with lymphoid interstitial pneumonia or PCP)
- Non Tuberculosis Mycobacteria Infection
- Lymphoma
- Hydatid disease

4. Rationale for this study

As described above, TB diagnosis in children is challenging in low-resource and conflict-affected settings, and a high number of children remain undiagnosed and untreated. A delay in TB diagnosis can lead to an increase in preventable morbidity and mortality.

Data from pilot studies in South Africa suggest that TB-focused POCUS improves timely diagnosis of childhood TB and is a valuable tool for monitoring treatment response. POCUS is widely distributed in MSF missions. POCUS as a non-invasive and low-cost imaging modality therefore has high potential to support TB diagnosis and monitoring of treatment in children. The study aims to refine and adapt TB-focused POCUS

protocols (i.e. FASH, Lung) for children with presumptive TB living in different TB endemic settings and with differing co-morbidities (i.e. HIV, malnutrition) and differential diagnoses (i.e. Cystic Echinococcosis).

Our future ambition is to incorporate POCUS in diagnostic algorithms for TB diagnosis in childhood, while adapting and simplifying the POCUS protocol to better adjust it to the local context.

5. Context

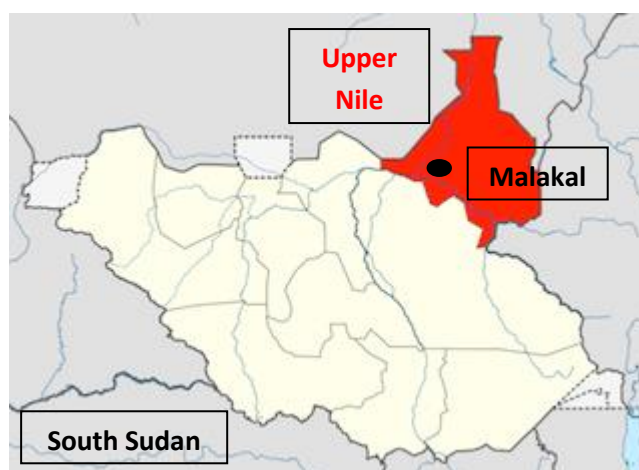
In 2016, 2.5 million people fell ill with TB in the African region, accounting for a quarter of new TB cases worldwide. An estimated 417,000 people died from the disease in the African region (1.7 million globally) in 2016. Over 25% of TB deaths occur in the African Region (46,47).

a. Malakal (South Sudan)

In South Sudan, TB remains a major public health problem. According to 2016 WHO data, the estimated TB incidence (all forms of TB) in South Sudan was 146 per 100.000 population (11% affecting children) in 2016, with an overall treatment coverage of 54%. HIV prevalence in the country and in Upper Nile region is 2.7%. Estimated rate of MDR TB in new and already treated cases is estimated to be 3 and 13% respectively (48). People living in IDP camps, have an increased risk to develop TB (49), and the estimated incidence in Malakal is 3.5 times higher than in the country, with high HIV co-infection (11%).

Médecins sans Frontières (MSF) started the intervention in Malakal (figure 1) by the end of 2013 due to a conflict crisis in the area which required big humanitarian needs. MSF is currently supporting primary and secondary health care in Malakal Protection of Civilians (POC) and Town, and supporting the rural area through a decentralised model of care. HIV/TB support started in 2015 and is currently supporting a cohort of around 100 HIV patients and is currently providing TB-DRTB integrated care. All components of the program (diagnostic, medical care, counselling and health promotion-community engagement) are supported by MSF, even if all data is reported to National TB Program according to MoH requirements.

Figure 1:



In 2017, a total number of 236 patients were diagnosed of TB and started on treatment. Among them, 34 (14%) were children, 14 among them under 5 years old. In 2018, the MoH placed Xpert MTB/RIF machine in MSF supported laboratory in Malakal POC. Improved diagnostic skills and community strategy with active case finding have increased the TB diagnosis by 25%, with 28 cases in the first 8 months of the year. POCUS was implemented by a specialized team during 2018 with specific training on FASH and Lung.

a. Bissau (Guinea Bissau)

In Guinea Bissau, TB remains a major public health problem. According to 2017 WHO data (50), the estimated TB incidence (all forms of TB) in Guinea Bissau was 374 per 100.000 population (15% affecting children) in 2017, with an overall treatment coverage of 32%. HIV prevalence in the country is 3.4% according to UNAIDS (51) and HIV coinfection in TB patients is as high as 32%. Estimated rate of MDR TB in new and already treated cases is estimated to be 2.5 and 14% respectively. The treatment success for new and relapse TB cases is 76 and 43% respectively. According to National TB Program data, in 2018 2200 persons were started on TB treatment and 45% among them were ≤ 15 years old.

MSF OCBA launched the permanent mission in Guinea Bissau (figure 2) in 2016 as a strategic choice with the objective to test and develop innovative medical strategies in paediatric care to decrease childhood mortality and which will ultimately help to overcome operational challenges, by being capitalized and exported to more unstable settings. MSF supports several departments in the Simão Mendes National Hospital in collaboration with MoH: paediatric intensive care unit (PICU), neonatal intensive care (NICU), in-patient therapeutic feeding centre (ITFC) and few beds in the paediatric ward. MSF is currently diagnosing TB in children and referring them to MoH / National TB program to initiate and continue treatment.

Figure 2:



POCUS was implemented during 2018 at Simão Mendes National Hospital and all training was provided by specialized team, including FASH and lung ultrasound.

6. Objectives

a. Main objective

To describe the findings obtained by POCUS methodology for pulmonary and extra-pulmonary tuberculosis in children per TB category.

b. Secondary objective

- 1) To establish the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of POCUS positive (any of 8 pre-established sonographic signs) as a composite against a composite reference of the final diagnosis (confirmed TB, unconfirmed TB or unlikely TB)
- 2) To describe the sonographic signs according to HIV status (positive, negative) and to nutritional status (SAM or not SAM)
- 3) To determine the proportion of children with improvement / resolution of sonographic signs and the proportion without improvement of sonographic signs at 2 months of follow-up in children with and without TB

- 4) To describe operational aspects of POCUS: compliance with POCUS examination; quality of POCUS; duration of POCUS; mean time to definitive diagnostic in POCUS positive results compared to POCUS negative results; proportion of children who started TB treatment on basis of POCUS positive results.

7. Patients and Methodology

a. Study design

We plan to conduct a multicentric study in 2 different centres: Malakal (South Sudan) and Bissau (Guinea Bissau). The methodology for the evaluation of POCUS for the diagnosis of TB in children will be longitudinal case series with diagnostic test evaluation.

b. Study sites

This study will be conducted in South Sudan in two different sites, the Malakal POC and the Malakal town, and in Bissau in one site, the Simão Mendes National Hospital.

c. Partnership and study coordination

In South Sudan, this study will be conducted in partnership between Médecins sans Frontières Operational Centre Barcelona-Athens (OCBA) and the Ministry of Health of South Sudan, in collaboration with the National TB Program. The MoH is willing to provide administrative and political support. The Xpert MTB/RIF machine was procured by MoH as well. No academic institutions have been involved in the study.

In Guinea Bissau, this study will be conducted in partnership between MSF OCBA and the MoH of Guinea Bissau, in close collaboration with the National TB Program. MSF works closely with MoH in Simão Mendes hospital, and the General Director of the TB hospital (Raoul Follereau Hospital), as well as the Responsible of the TB ambulatory care at Simão Mendes, are co-authors of the study and willing to provide technical support.

d. Study participants and sample size

1. Research population

The research population are children with presumptive TB in Malakal (town and POC hospitals) or in Bissau (Simão Mendes National Hospital).

Note that the same population will be offered to participate in the study “Evaluating Xpert MTB/RIF in stools and urine to improve TB diagnosis in children” which will be submitted in a separate protocol. Note that all participants will be asked to sign 2 separate consent forms.

2. Participants: inclusion criteria

- Any child from 6 months of life to 15 years old
- TB suspected according to diagnostic criteria
- Informed consent provided by legal responsible or companion

3. Participants: exclusion criteria

- Patients who have received TB treatment for > 1 day in the last 3 months

4. *Sample size*

The primary objective is to describe the findings obtained by POCUS methodology for pulmonary and extra-pulmonary tuberculosis in children per TB category. According to literature, POCUS positive as a composite (FASH and chest) have a sensitivity between 60 and 75% in EPTB and a sensitivity of 30 to 50% in PTB. An initial sample size was estimated assuming a sensitivity of 30% and precision of 12%, obtaining an initial sample size of 95 patients with TB (confirmed and unconfirmed); assuming that TB cases represented 60% of the cases, the global sample size of suspected TB was estimated in 158 patients.

In Guinea Bissau, 139 patients were enrolled, 89 with TB (27 of them confirmed) and 50 with unlikely TB up to April 2020 (recruitment was stopped 2 months in advance due to Covid-19). In Malakal, 39 patients were enrolled in a first phase in 2019-20 and recruitment stopped in January 2020 due to HR constraints and then Covid-19 and resumed in April 2020. By July 2021, 84 more patients were enrolled. Till then, POCUS was used as part of the diagnostic tools, thus a proper evaluation study required blinding POCUS results to clinicians and a new sample size has been calculated.

A new sensitivity of 70% has been assumed for the recalculation of the sample size. The sample size has been estimated with a variety of assumptions: we assume that TB confirmed and unconfirmed will represent 60% of suspected cases, sensitivity of 70% and precision of 10%. The sample size of TB as a composite will be 81 patients, therefore a total of 131 suspected TB patients will need to be included.

e. Definitions

a) SAM (severe acute malnutrition) in children (Appendix 14):

- Children < 5 years old: Z-score weight / height <-3 and / or MUAC <11.5 cm, and / or bilateral oedema.
- Children 5-15 years old: weight for height < 70% or bilateral oedema

b) HIV infection:

All patients with suspected TB will be tested for HIV, after consent of the legal responsible and pre-test counselling. The algorithm test will be adjusted to the age of the child (see **Appendix 10**). All children < 18 months will need PCR DNA for HIV diagnosis. All children ≥ 18 months and > 6 weeks of breastfeeding cessation will follow same diagnostic algorithm as for adults, which requires 3 positive rapid tests.

c) Suspected case of tuberculosis:

Any child with at least one of the following signs, symptoms or features is considered a **suspected case of tuberculosis** (Appendix 3):

- Persistent cough for more than 2 weeks
- Unexplained fever for more than a week
- Suspected extra-pulmonary tuberculosis (TBEP), e.g.:
 - Angular deformation of the spine (gibbous)
 - Lymphadenopathy
 - Subacute meningitis
 - Abdomen distended with ascites
 - > 2 weeks of diarrhoea
 - Painless enlarged joints
 - Pleural effusion

- Other

All **HIV positive** and **SAM children**, as well as all **TB contacts**, will systematically and actively be screened for TB.

Tuberculosis screening in children is done on admission and during hospitalization. If children are not identified as suspected TB cases at admission, a new assessment will be done after 1 week of admission. In addition to the above criteria, tuberculosis is suspected based on the following signs, symptoms and characteristics during hospitalization:

- Low weight gain despite correct nutritional treatment
- Persistent pneumonia or cough after adequate and well-followed antibiotic therapy
- Persistent fever (>38°C) beyond one week after exclusion from classical causes such as malaria or pneumonia
- Persistence or aggravation of fatigue
- Chest radiographs imaging suggestive of tuberculosis

d) Case with diagnosis of tuberculosis (52,53):

- **Confirmed TB:** patients with Xpert MTB/RIF positive (or TB culture positive when available) in a respiratory sample (pulmonary TB) or in other sample, such as CSF, lymph node or other tissue/liquid (extra pulmonary TB); TB LAM positive in HIV-infected patients.
- **Unconfirmed TB:** no microbiological confirmation but clinical diagnosis of TB and started on anti TB treatment (as established in Appendix 4).
- **Unlikely TB:** good response to other treatments (antibiotic, nutritional support, etc.) and no suggestive symptoms after 1 week of admission.

e) POCUS assessment:

Please, find below the definition of the main Chest and FASH sonographic signs:

FASH signs:

- Hepatic focal lesions: multiple small hypo-echoic lesions which represent TB micro-abscesses.
- Splenic focal lesions: multiple small hypo-echoic lesions which represent TB micro-abscesses.
- Ascites: free fluid in the abdominal cavity may be a sign of abdominal TB; sonographically free abdominal fluid is best investigated for in the Morison pouch, spleno-renal area and pelvis. In the TB-focused POCUS protocol FASH, presence of ascites only (without other abdominal pathology such as abdominal lymphadenopathy or hepatic or splenic focal lesions) is traditionally not considered sufficient to establish the diagnosis of abdominal TB (and POCUS would be reported as "negative").
- Abdominal lymph nodes: tuberculous abdominal lymphadenopathy is a common presentation of EPTB and can occur at different intraabdominal locations. Common locations that are easily accessible to POCUS are the epigastric region, splenic hilum region and mesenteric/paraaortal region. Abdominal lymph nodes larger than 1 cm diameter short axis are considered pathologic and

reported as abdominal lymphadenopathy.

CHEST signs:

- Sub-pleural nodules: sonographic multiple small (<1cm) hypoechoic nodules have recently been suggested as a possibly TB-specific finding; these may be present at various areas of the lung even in areas that appear normal on CXR.
- Consolidation: consolidated lung (sonographically presenting as hypoechoic tissue with or without air bronchograms) exceeding an area of 1 cm can represent local lung infection by TB or common bacterial pathogens causing pneumonia.
- Pericardial fluid: tuberculous pericarditis sonographically presents with free fluid between the visceral and parietal pericardium, which presents with an anechoic rim around the heart.
- Pleural effusion: tuberculous pleuritis sonographically presents with free fluid in the pleural cavity, which sonographically presents with anechoic areas commonly adjacent to the parietal pleura.

According to these findings, we can establish **POCUS positive vs. negative results:**

A) **POCUS positive and highly suggestive of TB:** presence of at least one of the following findings:

- 1) Subpleural nodules
- 2) Pericardial effusion
- 3) Abdominal lymphadenopathy
- 4) Focal splenic lesions

B) **POCUS positive and compatible with TB:** presence of any finding not including the findings above (pleural effusion, consolidation, focal hepatic lesions, ascites)

C) **POCUS negative:** if no suggestive sonographic signs present

8. Study procedures

a. Identification of participants

Eligible children will be identified upon admission to paediatric ward, ITFC, PICU/NICU (only in Bissau) or as suggestive cases in OPD. The identification of suspected TB cases will be mainly based on clinical criteria. A diagnostic algorithm (Appendix 4) will be applied to all suspected cases. The populations of interest for this study are hospitalized children, severely malnourished (SAM) and HIV positive or exposed children.

b. Laboratory

1. Sample collection

The medical team will follow a specific SOP for respiratory sample collection (naso-pharyngeal aspirate, gastric lavage or spontaneous sputum), lymph nodes (or other validated extra pulmonary samples) as described in the appendixes. In hospitalized children, all samples will be collected during hospitalisation. For ambulatory patients, samples will be collected within 2 hours in Observation.

2. Laboratory procedures

Xpert MTB/RIF will be performed on respiratory or extra pulmonary samples at baseline, and for those with negative results and persistent symptoms, will be repeated after 1 to 2 weeks. TB LAM will be done on all HIV-infected patients.

c. POCUS assessment

At least two medical national staff is trained on POCUS performance using FASH and chest methodologies. Training was executed in two different rounds and staffs capable of performing the POCUS independently have been identified. The detailed procedures for performing the point of care ultrasound examination are documented in the POCUS MSF protocol. Results of the point of care ultrasound examination will be documented in the POCUS study report form (Appendix 15) for study purposes and on a POCUS form which will be kept with the patient file for clinical management; the POCUS form will be provided to the attending medical staff immediately after the POCUS examination. All patients will have a POCUS done at baseline and after 2 months.

As per routine, all patients are discussed with Expat Medical Doctor who supports and supervises the national team in patient management. On top of that, all patients' summaries and POCUS images and clips will systematically be posted on the Telemedicine platform and discussed with both the POCUS expert, Sabine Bélard, and the TB expert, Laura Moretó.

In order to achieve the objectives, the following information will be collected:

- POCUS positive or negative (as described in section "Definitions")
- Time to final diagnosis (confirmed TB, unconfirmed TB, unlikely TB)
- POCUS interpretation (suspicion of TB or not) and impact on decision making
- Sonographic signs after 2 months of follow-up: improvement / resolution vs. no change in sonographic signs

In the first part of the study, POCUS has been used to support TB diagnosis in a total of 262 patients (139 in Bissau and 123 in Malakal). Starting from July 2021, POCUS results have been blinded to the Clinician, to ensure proper evaluation of the diagnostic tool.

The concordance between the operator and the POCUS expert will be recorded, and all cases of discordance will further be evaluated by a third reader.

d. Linkage to care for HIV/TB patients

All patients HIV positive will be enrolled into HIV care either in MSF program (Malakal) or MoH programs (Bissau). MSF will guarantee that all children will be started on ART after 2 weeks of TB treatment (or as soon as possible if TB has been excluded) or differed to 4-6 weeks in case of TB meningitis.

All TB cases (confirmed or unconfirmed) will be enrolled in TB care in MSF program (Malakal) or MoH program (Bissau). MSF will ensure that all patients to be started on adequate weight-based dose fix combinations and followed up during the length of treatment. All children diagnosed of DRTB will be initiated on DRTB treatment regimen according to national recommendation.

e. Follow-up patients and tracing of defaulters

All TB patients will be followed up for the duration of the treatment. The clinical appointments will take place according to TB program requirements. After the initial assessment, all study participants will have a follow-up appointment at month 2 to perform a follow-up POCUS (regardless of TB treatment).

All patients included in the study (including those with unlikely TB) will provide telephone number (if available) and address. Whenever possible and if accepted by parent or guardian, a community health worker (CHW) will accompany the patient home after discharge. This CHW will be responsible for tracing the patients not attending the follow-up appointment. The CHWs are part of the Health Promotion / Community Engagement team and routinely involved in tracing of defaulters, including HIV/TB patients.

Transportation fees will be covered for patients requested to attend consultation outside of the appointments stipulated for conventional follow-up of TB (ie. patients with unlikely TB who need to attend after 2 months of discharge).

f. Data collection

The following information will be noted in an individual case study report form (CRF) for each participant:

1. DEMOGRAPHIC INFORMATION AND INFORMED CONSENT OF PATIENTS:

- Study code
- Date of birth / age
- Sex
- Parent or guardian's informed consent: Yes / No
- Consent to be traced in case of defaulting

2. CLINICAL AND DIAGNOSTIC INFORMATION OF STUDY PARTICIPANTS AT BASELINE AND DURING FOLLOW-UP:

- Entry point (OPD, TB or HIV or Nutrition program, IPD)
- History of TB contact, HIV or malnutrition
- Temperature (axillary) (°C)
- Weight and size
- Nutritional status
- Co-morbidities: malaria, respiratory infection, HIV status
- Signs and clinical symptoms suggestive of tuberculosis
- Final diagnosis
- TB treatment started: Yes / No
- Date of TB treatment started
- Follow-up information at month 2 and 6
- TB treatment outcomes

3. LAB EXAMS INFORMATION:

Lab information will be recorded using the Lab form in the study “Evaluating Xpert MTB/RIF in stools and urine to improve TB diagnosis in children”.

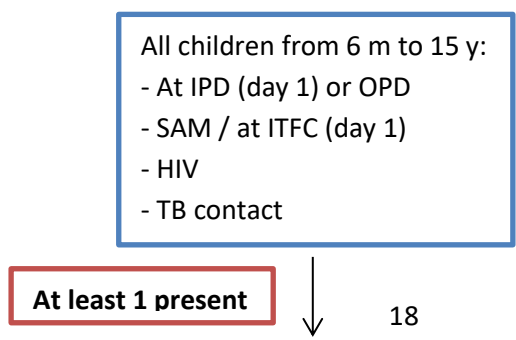
4. POCUS INFORMATION (BASELINE AND AT MONTH 2):

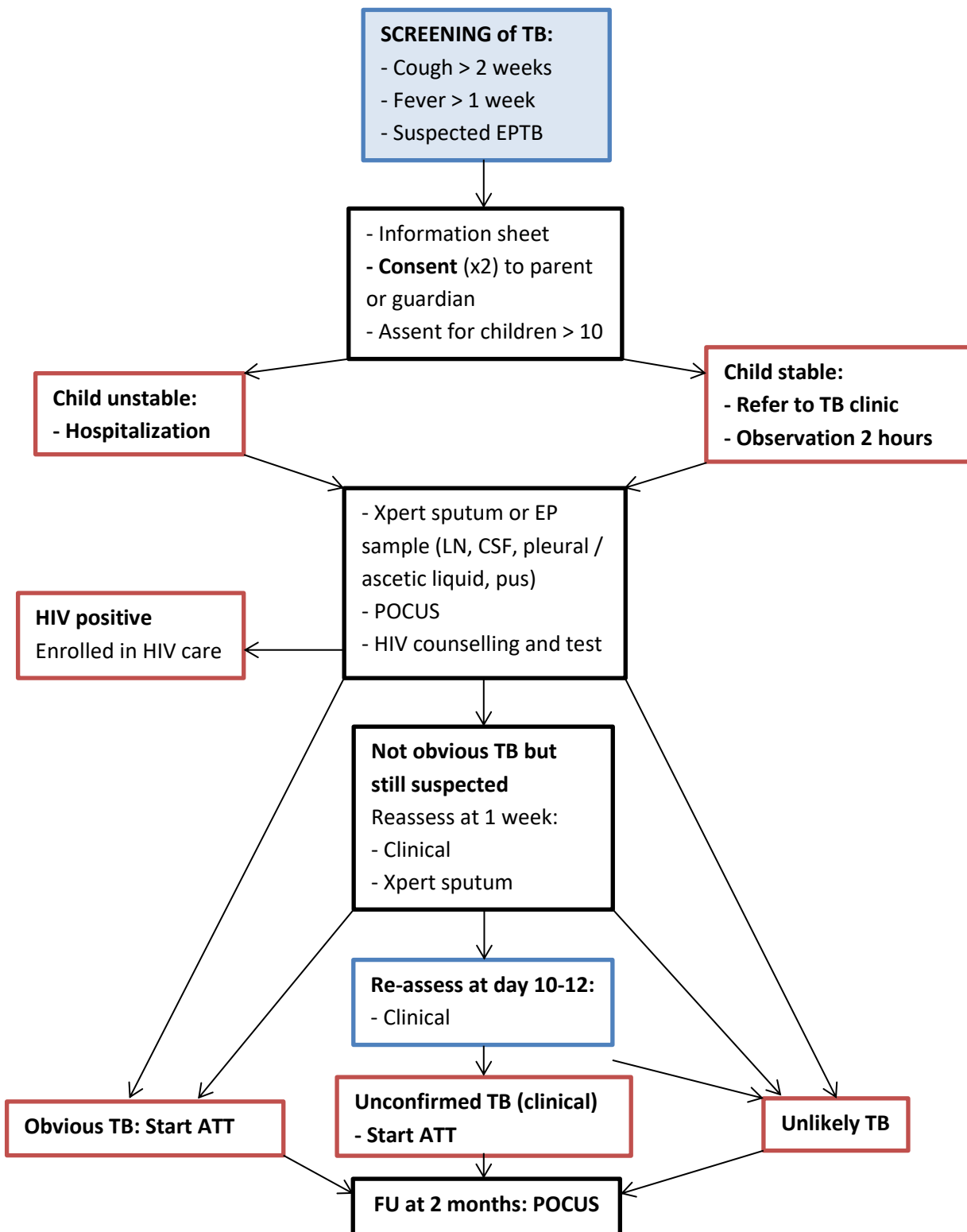
- Date of POCUS chest and FASH exam
- POCUS positive: presence of 1 or more suggestive sonographic signs described below
- FASH signs:
 - Hepatic focal lesions
 - Splenic focal lesions

- Ascites
- Abdominal lymph nodes
- CHEST signs:
 - Pleural line
 - Consolidation
 - Pericardial fluid
 - Pleural effusion
- Patient's compliance with POCUS:
 - Good: patient was cooperative and remained calm
 - Moderate: patient was crying but remained calm
 - Bad: patient was crying and moving
- Every sonographic sign/assessment will be rated with one of the following options:
 - Yes: target pathology present
 - No: target pathology not present
 - Not evaluated/not evaluable (NE)
- Duration of the examination:
 - < 10 minutes
 - 10-20 minutes
 - 20-30 minutes
 - > 30 minutes
- Date and time point of POCUS: day (D0, D1...) on which the POCUS was performed
- Interpretation of POCUS:
 - Positive with high suspicion of TB
 - Positive with low suspicion of TB
 - Negative (no suspicion of TB)
- Impact on decision making:
 - No change in diagnosis or therapeutic management
 - Changed diagnosis or therapeutic management
 - Repeat POCUS scan after 2 weeks
- Follow-up POCUS after 2 months:
 - Resolution of sonographic signs
 - Improvement of sonographic signs: decrease in size of lesions
 - No change in sonographic signs

g. Flow of patients

OPD patients who don't need hospitalization will be requested to stay in observation for 2 hours to perform all initial exams (including POCUS) after obtaining the informed consent, but all diagnostic process and follow-up will take place at the external consultation.





9. Safety Considerations

There are safety considerations related to infection control of TB, even if children are only considered contagious after they acquire the capacity of expectorating (> 8 years old). For older children, isolation procedures for coughing patients, as well as protection measures for medical staff, need to be implemented. Lab staff needs to wear respirator and gloves when manipulating samples for Xpert MTB/RIF. Safety procedures related to Xpert MTB/RIF need to be in place.

Diagnostic procedures are routinely done in all children with suspected TB (on not specifically for the study). Gastric lavage and naso-pharyngeal aspirate can be uncomfortable. For gastric lavage, there's a small risk of spasms of vocal cords, tube entering in the airway instead of the oesophagus, minor bleeding or aspiration pneumonia. Regarding naso-pharyngeal aspirate, the actual risks for participants are still smaller; it can cause nausea or local annoyance. Lymph node puncture is a routine procedure as well and is only performed in palpable lymph nodes (≥ 2 cm). The risks are small and can comprise blood vessel puncture or accidental exposure to blood for the staff. All three are common procedures which will only be performed by trained staff. Any possible complication will be treated by MSF.

No specific additional safety considerations related to POCUS.

10. Data Management and Analysis

The number of children tested by the program for suspected tuberculosis, the number of eligible children and the number of cases included in the study during the recruitment period will be noted. The number of parent or guardian of eligible children who refuse their participation will also be registered. Demographic, clinical and diagnostic characteristics at baseline and during patient follow-up under the program will also be recorded.

Data will be collected in the files by the study team members. Data will be coded and entered into a RedCap database and analysed with SPSS software. Continuous variables (e.g. age, distance) will be summarized using mean and standard deviation or median and interquartile range as appropriate and may also be expressed as ordinal categories with frequencies; frequencies will be reported with corresponding 95% confidence intervals. The main outcome of interest for POCUS study is to describe the findings obtained by POCUS methodology for pulmonary and extra pulmonary tuberculosis in children.

Bivariate analysis is planned for TB (confirmed and unconfirmed) vs unlikely TB, HIV positive vs. HIV negative, and for SAM vs. not SAM. Children with HIV and SAM will be considered as a confounder. Comparisons of these categorical variables across groups will use Chi-squared or Fisher's exact test. All estimates will be presented with respective 95% confidence intervals. Cohen's kappa coefficient will be used to determine the inter reader agreement of TB-focused POCUS positive, negative and per sign between the operator and second reader, and third reader in case of disagreement.

The number of children screened for suspected tuberculosis, the number of eligible children and the number of cases included in the study during the recruitment period will be noted. The number of parents or guardians of eligible children who refuse their participation will also be registered. Demographic, clinical and diagnostic characteristics at baseline and during patient follow-up under the program will also be recorded.

Data analysis of the study will be conducted by the Epidemiologist/Statistician involved in the study, in collaboration with the PI.

11. Ethical Considerations

The study will be conducted in accordance with the Declaration of Helsinki on Ethical Principles of Medical Research on Human Subjects, and in accordance with the rules of the National Ethics Committee of South

Sudan and Guinea Bissau. The protocol will be submitted for approval to the National Committee for Ethics of South Sudan and Guinea Bissau, and the MSF Ethics Committee.

a. Informed consent

Participation in the study is on a voluntary basis and requires prior informed consent. Trained staff will provide eligible parents or guardians with detailed information on the study's objectives and procedures, as well as a clear explanation of the risks and benefits of participation. A written information sheet will be given to the parents or guardians, in English or in local language (appendix 1). The study staff will assist the parents or guardians on all the points indicated in the form and answer all the questions. If the parent or guardian is not able to read the information sheet, staff should read it aloud.

All children will be briefed on the study and the information will be adjusted to the age range and an assent process will take place for children older than 10 years old, but following national legislature, the consent must be signed by an adult. All questions will be answered by medical staff responsible for the study.

Parents or guardians agreeing to have their child participating in the study will need to sign an informed consent, which will also be signed by the study staff. For illiterate parents or guardians, a witness who can read and write, designated by the parent or guardian himself and who will not be a staff member of the study, will be present throughout the information process and will co-sign the form to confirm that the parents or guardians has understood and willingly accepts participation in the study.

The process of informed consent will be done in an area of the clinic that offers enough privacy to make a voluntary decision without constraint. Parents or guardians will be explicitly informed that they have the right to refuse participation or withdraw from the study at any time during the research. Copies of both forms (ie. the study information sheet and informed consent, in English or in the local language) will be given to the parents or guardians.

b. Confidentiality

All information collected during the study will be recorded and identified by a specifically assigned number for the study and the number assigned routinely for the program. Patient or parents or guardians names will not be recorded in the study form or electronic databases. Access to the study information (in paper or electronic format) is restricted to authorized staff.

Home visits are part of the regular work of CHWs, who have specifically been trained for this task. To guarantee confidentiality, they are not informed about the reason of the visit and just deliver a request to attend the clinic as soon as possible. This information has been shared with the local authorities and is routinely explained to all patients prior to asking for consent for home visits.

Informed consent forms will be kept in a secure and confidential place in a locked cabinet by the study coordinator throughout the study. The consent forms will be archived for a minimum of 5 years after the end of the research, in a secure and locked archive by the investigator at MSF OCBA, in Barcelona. After this period, all documents will be destroyed. If the Ministry of Health requests to archive copies of the informed consents, they will be given at the end of the research study.

c. Benefits

We expect that the study will contribute to a better definition of an appropriate pediatric POCUS protocol for childhood TB in different settings. Improved tools for paediatric TB diagnostic will ultimately have an impact in improving TB diagnosis in children and reducing mortality in paediatric TB.

We expect that the results of the study will build the base of an improved diagnostic strategy in which diagnostic tools are more adapted to a particular operational/epidemiological context.

At an individual level, a potential benefit would be a most efficient diagnosis of TB in the child, which will lead to an earlier treatment and improved prognosis. All patients will be included in the TB (and HIV when required) program. The community will benefit of the improved TB detection in children.

d. Risks

The potential risk for the implementation related to the study is eventual challenges in manipulation of TB samples. The risks linked to the field might be instability of the context and lower recruitment rate than expected which would lead to a longer duration of the study.

Regarding the potential individual risks for the subjects in the study could be a longer stay at the hospital. The POCUS and the sample collection are not invasive, therefore no expected harms due to this procedure. No harms have been identified at community level. The risks related to sample collection are described in section 9 and can be related to gastric lavage, naso-pharyngeal aspirate or lymph node puncture; these procedures are used routinely for the diagnosis and not specifically for this study.

Being diagnosed of TB can be associated to stigma. MSF has been supporting the TB program in Malakal for the last 3 years and a health promotion and community engagement strategy to increase knowledge and reduce stigma is already in place; an assessment on TB related stigma showed that stigma on TB is relatively low in the area. In Bissau, the National TB Program is responsible for TB treatment initiation and follow-up. TB stigma in the capital was evaluated as low. Moreover, all children in both settings will be treated with strict confidentiality.

12. Timeline

The estimated overall duration will be 36 months, starting from January 2019, 28 of them in the field:

- Ethical review: 2 months
- Training to staff: 1 month
- Inclusion and data collection: 24 months
- Data analysis and report: 3 months
- Dissemination: 6 months

13. Dissemination of Results and Publication Policy

Programme results will be presented to MoH authorities, as well as to WHO, to advocate for the use of POCUS in the TB diagnosis in children if the study show promising results and added value in the TB diagnosis.

The results of the study will be presented in conferences and published in a peer reviewed journal in order to share results with the TB public health professionals and other medical-humanitarian actors.

14. Budget needs

Costs related to the study are guaranteed by MSF operational budget, including necessary human resources and all consumables and diagnostic tests, which will be available through standard MSF procurement and supply mechanisms.

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16. Appendixes

Please, note that many of the following appendixes will be used for the study “Evaluating Xpert MTB/RIF in stools and urine to improve diagnosis in children”. Only the appendixes marked with an asterisk are specific for this study:

Appendix 1: Study Information Sheet: POCUS*

Appendix 2: Informed Consent Form POCUS*

Appendix 3: Clinical form (CRF)

Appendix 4: TB diagnostic algorithm (SOP of TB diagnosis in children)

Appendix 5: SOP for naso-pharyngeal aspirate

Appendix 6: SOP for gastric lavage

Appendix 7: SOP for pulmonary sample collection, storage and shipment

Appendix 8: SOP for lymph node puncture and Xpert MTB/RIF assay

Appendix 9: SOP for Xpert MTB/RIF assay performance

Appendix 10: SOP for the diagnosis of HIV in children

Appendix 11: Checklist for adherence counselling (HIV and TB)

Appendix 12: Anti-TB dosages for children

Appendix 13a: Weight for height from 5 to 10 year old

Appendix 13b: Weight for height in adolescents (10 to 18 year old)

Appendix 14: POCUS report form*

Appendix 1: Study Information Sheet POCUS

Title of the study: EVALUATING POINT OF CARE ULTRASOUND (POCUS) TO IMPROVE TB DIAGNOSIS IN CHILDREN

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Version: version 1.11, March 2019

Dear Sir or Madam,

Médecins sans Frontières (Operational Centre Barcelona-Athens - OCBA) and the Ministry of Health, invite you to participate with your child in a study to evaluate Xpert MTB/RIF in stools and urine to improve the diagnostic of TB in children. Before making your decision and accepting or refusing to participate, it is important that you understand this information sheet which explains several aspects of the study. You can read it, or we can read it and explain it to you, and we will answer any questions you wish to ask.

Please, note that we will also offer your child to participate to the research “Evaluating Xpert MTB/RIF in stools and urine to improve diagnosis in children” and a separate information sheet and consent form will be shared with you as well. Please note that it is your decision whether to participate only in one of the studies, both studies or not at all, without any consequences.

All the relevant information will be shared also with your child adjusted to age range and all questions will be answered, but for ethical reasons we ask you to sign the consent form.

Background and purpose of the study: Tuberculosis (TB) is a very common disease but its diagnosis is difficult, especially in children. Point of care ultrasound (POCUS) has been studied for TB diagnosis in children but there is still a need to collect more data on the utility of the test. POCUS is done by a trained medical professional, it’s a non-invasive and bedside procedure, and it usually takes less than 30 minutes. We hope that this research will help improve the diagnosis of tuberculosis in children Malakal, South Sudan, as well as in other places where resources are limited.

Why are you asked to participate? We want your child to participate because he/she meets all the criteria of the study: he/she is between 6 months and 15 year old, he/she presents the symptoms of tuberculosis and he/she has not been treated for TB in the last 3 months.

What happens if you participate in the study? If you agree to participate in the study, your child will be examined as normally done in that hospital, and will be given all the usual tests for the diagnosis of tuberculosis. In addition, a POCUS study will be performed on him/her. The result of the POCUS will only be used for the study, because it is not yet known whether this test works well in children. The usual treatment

for tuberculosis, like any other necessary treatment, will normally be given to your child, according to the MSF and national recommendations. Your child will be followed during the whole duration of the treatment as part of the TB program and regardless of the participation in the study. You will be requested to come back to the facility after 2 months to repeat POCUS.

Do you have the right not to participate? Participation in the study is left to your decision alone. You are free to decide whether your child will participate in the study or not. You are also free to withdraw your child from the study at any time. Your decision will not affect the care your child will receive at this hospital.

Are there disadvantages and risks if you participate in the study? Participation in the study entails no risk. The rest of procedures are routinely done (not specifically for the study).

What are the advantages if you participate? There are no direct benefits for you or your child if he/she participates in the study. But your child's participation in the study will improve the diagnosis of TB in the future, and we hope to be able to better manage TB in children. You will not receive any direct monetary benefit such as food or payment as a reward for participating in the study. Only children without TB requested to come back after 2 months to repeat POCUS will have transportation reimbursed.

Is confidentiality assured? All information we collect about your child during the course of the study will remain strictly confidential. Your child's name will not appear on the study documents or on the reports. All documents will be kept in a locked cupboard and only staff working for the study will have access to the information that will be collected.

How will the results of the study be used? The results of this research will be shared within MSF and with experts at the national and international levels in both national and international meetings, and will be published in specialized medical journals. All available results will be shared with you as well.

Who did verify and approve the study? This study was verified by the National Ethics Committee of South Sudan and by the MSF Ethics Committee.

If you agree to your child's participation in the study, please sign with your name below indicating that you have read and understood the nature of the study, your responsibilities as a participant, the risks and benefits associated with your free and voluntary participation, and that all your questions about the study have been answered satisfactorily.

You will receive a copy of this consent form once it is signed, which you can keep at home.

Assent process for children older than 10 years old:

There's a disease called Tuberculosis which is quite common in the area where you live but unfortunately diagnostic is difficult and many children remain without diagnosis. This is the reason why we are proposing a study to evaluate your abdomen and test by an ultrasound.

Your parent or guardian said it would be all right for you to take part of this study but this is your decision. If you don't want to participate, you don't have to and if you want to stop it at any time, just let us know and we will proceed accordingly. We will ask you to participate to a second study that wants to evaluate Xpert in stools and urine, and you can accept to participate in both, in only one or in none of them.

If you agree to help us, we will ask you to do an ultrasound today and in 2 months. Normally, it doesn't take more than 30 minutes to perform and it is not painful.

If you sign or mark this document it means that you understand the information I just explained and that you agree to be part of the study. If you don't want, don't sign the document.

The above statement has been read to the child and he agrees to participate in the study.

The child accepts participating in the study: Yes No

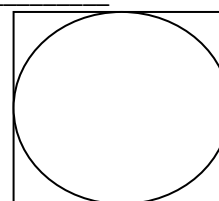
Appendix 2: Informed consent form POCUS

Declaration of the parent or guardian of the participating child

I confirm that I received orally and in writing all the information concerning this study, and that I understood what is asked if I participate. I know who to contact if I need more information about this study. I understood that the personal information will remain confidential throughout the study and that I have the freedom to stop the participation of my child at any time without this modifying the care s/he receives / will normally receive in the clinic.

I accept that my child under my care is participating in this study. I will receive a copy of this informed consent to keep.

Name of child participating in study: _____



Date Nameparent/guardian Signature or thumbprint
If caretaker can't read or write

Date Name of staff Signature

Date Name of the witness Signature
If parent/guardian can't read or write

Contact persons for further information

If you have a problem or have questions about this study, you can contact the staff collaborating in the study directly, and also contact:

Laura Moretó, Principal Investigator in the Study
MSF OCBA, Medical Department
Tel: +34 93 304 6168
Email: laura.moreto@barcelona.msf.org

Note that this form will be shared between the 2 studies (Xpert MTB/RIF stools/urine & POCUS) and only filled once

Appendix 3: CRF clinical form

Background information of study participant Date: / /

Study code patient:
 Date of birth: _____ Age: _____
 Sex: Female Male
 Parent or guardian's informed consent: Yes No
 Consent to be traced in case of defaulting: Yes / No

Baseline clinical information at entry of study Date: / /

Entry point to study:

OPD <input type="checkbox"/>	TB program (ie. TB contact) <input type="checkbox"/>
IPD <input type="checkbox"/>	HIV program <input type="checkbox"/>
Nutrition program <input type="checkbox"/>	other <input type="checkbox"/> Specify: _____

Screening in all children, HIV, SAM or TB contacts:

Fever > 1 week <input type="checkbox"/>	
Cough > 2 weeks <input type="checkbox"/>	
Suspected extra pulmonary TB <input type="checkbox"/>	Site: _____

Screening in all hospitalized children after 1 week hospitalisation if suggestive symptoms:

Loss weight despite correct nutritional treatment <input type="checkbox"/>
Persistent cough or pneumonia despite antibiotic <input type="checkbox"/>
Persistent fever once classical causes excluded <input type="checkbox"/>
Persistent or aggravated fatigue <input type="checkbox"/>
Chest radiography suggestive of TB <input type="checkbox"/>

History of:

TB or chronic coughing contact: Yes <input type="checkbox"/> No <input type="checkbox"/>
Unexplained weight loss in the last 3 months <input type="checkbox"/> MAM <input type="checkbox"/> SAM <input type="checkbox"/>
Known HIV status: Negative <input type="checkbox"/> Positive <input type="checkbox"/> Unknown <input type="checkbox"/>

Clinical condition:

Temperature (axillary) (°C): _____	Weight (kg): _____	Size (cm): _____
Nutritional status: Not significantly malnourished <input type="checkbox"/>	MAM <input type="checkbox"/>	SAM <input type="checkbox"/>
Co-morbidities:		
Malaria	Respiratory infection:	
HIV: Negative <input type="checkbox"/> Positive <input type="checkbox"/>	Unknown <input type="checkbox"/>	
First PCR DNA pending <input type="checkbox"/>	Confirmation PCR DNA pending (first positive) <input type="checkbox"/>	
ART regimen: _____	Date ART started: / /	
Signs of pulmonary TB:		
Cough <input type="checkbox"/>		
Tachypnea <input type="checkbox"/>		
Hypoxemia (sat O2 < 92%) <input type="checkbox"/>		
Fever (axillary temperature > 38°C) <input type="checkbox"/>		
Signs of extra pulmonary TB:		
Angular deformation of the spine (gibbous) <input type="checkbox"/>		
Lymphadenopathy <input type="checkbox"/>		
Subacute meningitis <input type="checkbox"/>		
Abdomen distended with ascites <input type="checkbox"/>		

> 2 weeks of diarrhoea	<input type="checkbox"/>	
Painless enlarged joints	<input type="checkbox"/>	
Pleural effusion	<input type="checkbox"/>	
Other	<input type="checkbox"/>	Specify:
POCUS done: Yes <input type="checkbox"/> No <input type="checkbox"/>	Date:	/ /

Information at discharge: final diagnosis	Date: / /
--	------------------

Confirmed pulmonary TB	<input type="checkbox"/>	
Suspected pulmonary TB	<input type="checkbox"/>	
Confirmed extra pulmonary TB	<input type="checkbox"/>	
Suspected extra pulmonary TB	<input type="checkbox"/>	
Unlikely TB	<input type="checkbox"/>	
Other	<input type="checkbox"/>	Specify:

TB treatment	
Started: Yes <input type="checkbox"/> No <input type="checkbox"/>	Date ATT started: / /
Regimen:	

Follow-up after 2 months of discharge (POCUS participants)	Date: / /
---	------------------

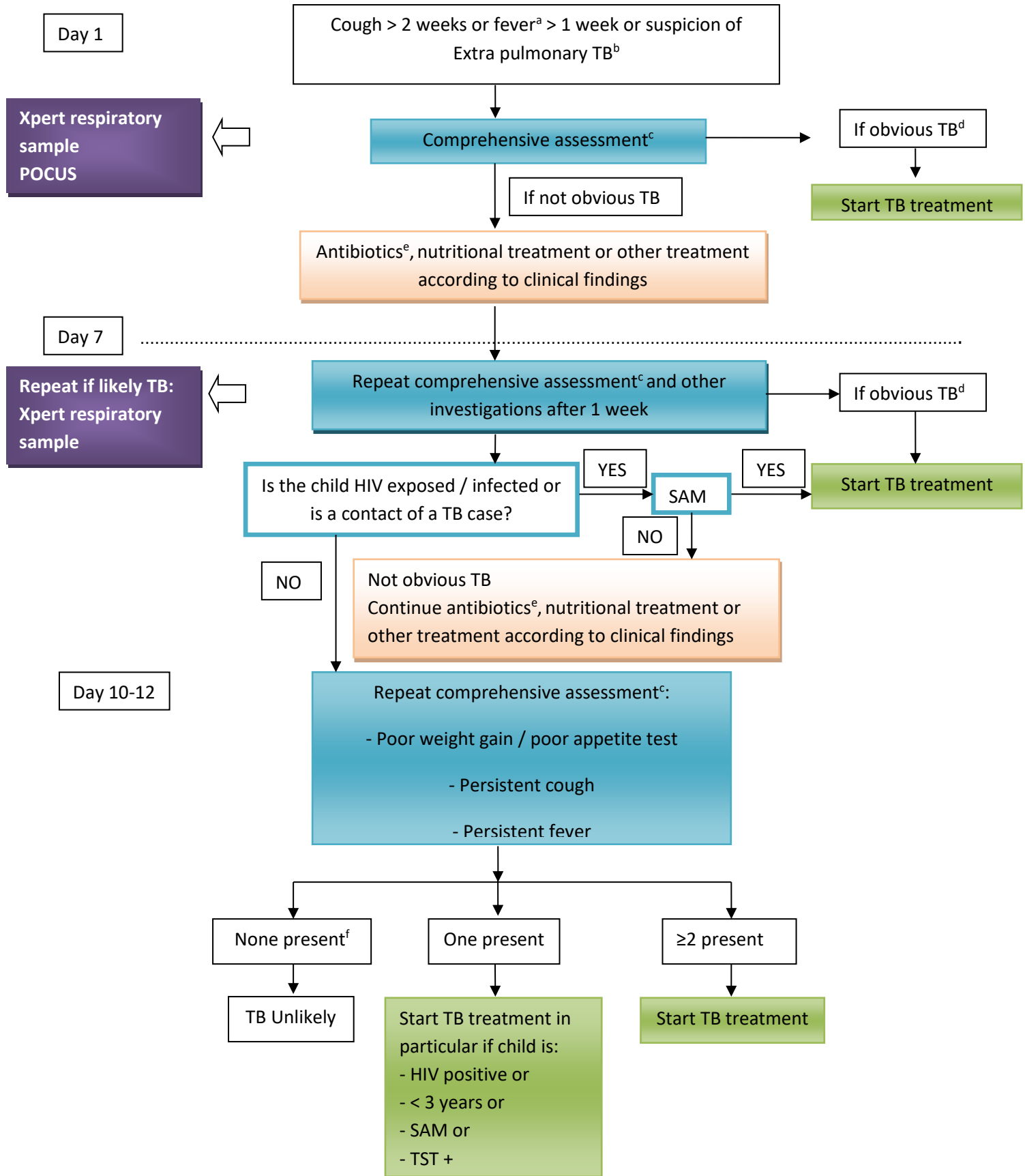
Nutritional status:	Not significantly malnourished <input type="checkbox"/>	MAM <input type="checkbox"/>	SAM <input type="checkbox"/>
TB treatment prescribed:	Yes <input type="checkbox"/>	No <input type="checkbox"/>	
Under TB treatment:	Yes <input type="checkbox"/>	No <input type="checkbox"/>	
If interruption, specify reason:			
Smear at month 2:	Done <input type="checkbox"/>	Positive <input type="checkbox"/>	Negative <input type="checkbox"/>
	Not done <input type="checkbox"/>		
POCUS done:	Yes <input type="checkbox"/> No <input type="checkbox"/>	Date:	/ /

TB patients: follow-up after 6 months of discharge (POCUS participants)	Date: / /
--	------------------

Nutritional status:	Not significantly malnourished <input type="checkbox"/>	MAM <input type="checkbox"/>	SAM <input type="checkbox"/>
TB treatment finalised:	Yes <input type="checkbox"/>	No <input type="checkbox"/>	
Smear at month 6:	Done <input type="checkbox"/>	Positive <input type="checkbox"/>	Negative <input type="checkbox"/>
	Not done <input type="checkbox"/>		
POCUS done:	Yes <input type="checkbox"/> No <input type="checkbox"/>	Date:	/ /

TB treatment outcomes:		
Cured: <input type="checkbox"/>	Defaulted: <input type="checkbox"/>	Date: / /
Completed: <input type="checkbox"/>	Death: <input type="checkbox"/>	
Failure: <input type="checkbox"/>	Not evaluated: <input type="checkbox"/>	

Appendix 4: TB diagnostic algorithm



- a) Axillar temperature > 38°C
- b) Enlarged lymph nodes, gibbous, > 2 weeks diarrhoea, meningitis
- c) Comprehensive assessment includes:
 - a. Clinical assessment
 - b. Growth assessment
 - c. Bacteriological test (sputum collection, naso-pharyngeal aspirate, gastric lavage, lymph node aspiration):
 - Xpert MTB/RIF testing (sputum, nasopharyngeal aspirate, gastric lavage, lymph node aspirate, CSF);
 - Xpert MTB/RIF in stools and urine;
 - TB culture and DST (only at baseline):

For children:

 - < 5 years old: do nasopharyngeal aspirate (Appendix 5)
 - From 5 years old until child can expectorate: gastric lavage (Appendix 6)
 - For children who can expectorate: sputum
 - d. POCUS (only at baseline)
 - e. HIV testing if not yet performed (Appendix 16)
 - f. When relevant and available: X-ray (CXR, spine)
- d) Xpert MTB/RIF positive, CXR showing suggestive lesions (e.g. hilar lymphadenopathy, upper lobe infiltrates, and miliary picture), gibbous.
- e) Broad spectrum antibiotics:
 - **If no signs of severity:**
 - First line: amoxicillin PO for 7 days (NO fluoroquinolones)
 - If a second course of antibiotics is needed: azithromycin PO for 5 days
 - **If signs of severity:**
 - Parenteral antibiotics (ceftriaxone ± cloxacillin if *S.aureus* is suspected)
 - If a second course of antibiotic is needed: azithromycin PO for 5 days
 - In addition: **PCP treatment** should be given presumptively to all HIV-exposed or infected children < 1 year of age and any older child with severe immune suppression and not on CTX prophylaxis. For all other HIV-exposed or infected children, it should be considered if there is poor response to broad spectrum antibiotics after 48 h
- f) Clinical response to broad-spectrum antibiotic does not rule out TB. Continue follow up to see if symptoms re-occur

Appendix 5: SOP for naso-pharyngeal aspirate²

Equipment required:

- Disposable gloves and respirator masks (N95)
- Suction apparatus
- Sterile 6/7/8 G mucus extractor or nasogastric catheter
- Normal saline (0.9%) 5 ml
- Sterile syringe 50 ml (single use)

Performing nasopharyngeal aspiration:

1. Infection control measures: All personnel responsible for collecting respiratory specimens must wear personal protective equipment. The procedure will take place in a dedicated cough room or should be fitted with a door that can lock and windows that open to the outside. Alternatively, samples may be collected outside in the open air or in sputum collection booth/other appropriate structure housed outdoors.

2. The child's nose is cleaned with saline drops. If old enough, the child can be asked to blow the nose into a tissue. If the nasal mucus is too thick to be removed with the measures above, it can be suctioned prior to nasopharyngeal aspiration. A soft catheter size F6/7 is used for suctioning and is discarded immediately afterwards.

4. Two drops of sterile saline are instilled into each nostril.

5. The length of the cannula used for aspirating the NPA sample is measured as the distance from nostril to tragus of the ear; then the posterior nasopharynx is suctioned using a soft plastic cannula connected to a mucus trap.

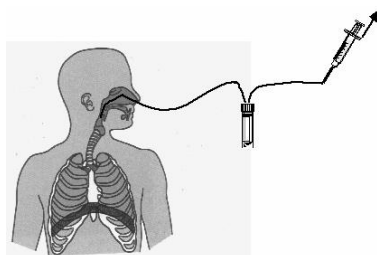
6. Suctioning is activated only when the tip of the cannula is in the posterior nasopharynx. When the cannula is passed through the nostrils (during introduction and extraction), the suction is de-activated.

7. Transfer full volume of sample into a sterile container (Falcon tube).

8. Clean Falcon tube with alcohol swabs.

9. Label sample: sample type and number, date, time, total sample volume.

10. Place specimen in sample bag, seal and put into a cold box for transport to lab.



² Based on SOP collection of respiratory specimens in children, Desmond Tutu TB Centre Paediatric Studies

Appendix 6: SOP for gastric lavage³

Equipment required:

- Gloves and respirator
- Suction catheter (6, 7, 8F)
- Sputum container
- 50 ml syringe
- Sterile water

Performing gastric lavage:

1. Infection control measures: All personnel responsible for collecting respiratory specimens must wear personal protective equipment. The procedure will take place in a dedicated cough room or should be fitted with a door that can lock and windows that open to the outside. Alternatively, samples may be collected outside in the open air or in sputum collection booth/other appropriate structure housed outdoors.
2. Child needs to be fasting for at least 4 hours and the procedure will take place early in the morning.
3. Place the child in a half-sitting or sitting position in the adult's arms.
4. Insert a nasogastric tube and check that it is correctly placed.
5. First suction to collect the gastric fluid and place it in the sputum container, then rinse the stomach with 30 ml of sterile water and suction again. Add the suctioned fluid to the first sample.
- 6.

³ Based on SOP of sputum collection in MSF TB guidelines 2014

Appendix 7: SOP for pulmonary sample collection, storage and shipment

Sputum collection techniques:

Regardless the collection technique used, staff member present during sputum collection should wear a respirator to prevent bacilli inhalation.

Sputum obtained spontaneously:

Two specimens are to be collected. When possible, specimens should be collected outside in the open air and far away from other people.

The first sample is collected on the spot, at the consultation, when the patient is identified as suspected TB case. If the patient has recently eaten, ask him/her to rinse his/her mouth with water in order to avoid the presence of food in the sample.

The second sample is collected the day after, in the early morning, right after the patient wakes up and before eating. The second sample may be collected at home then the patient brings it to the health facility.

Alternatively, two sputum specimens can be collected one hour apart (frontloaded microscopy). Collection technique:

- The patient must be given a labelled sputum container (or a Falcon® tube, if the sample is to be shipped by air).
- Have the patient take a deep breath, hold for a few seconds, exhale, repeat two or three times, then cough: sputum is material brought up from the lungs after a productive cough. One or two minutes of chest clapping are of benefit.
- Collect at least 3 ml and close the container hermetically.

The quality of sample determines the reliability of the result. Always check that the sample contains solid or purulent material and not only saliva. Take a new sample if unsatisfactory.

If the sample is collected at home, make sure that the patient has understood the technique, including closing the container hermetically after collecting the sputum.

Sputum specimen storage

When examinations are not performed on the site of collection:

- **Specimen for smear microscopy**

Smears should be performed within three-four days of collection and in the meanwhile stored refrigerated (2 to 8°C) and protected from light.

Contamination does not affect microscopy but heat make specimen liquefy, with selection of mucopurulent part of the sample more difficult.

- **Specimen for culture in liquid medium**

Keep the specimen refrigerated (2 to 8°C), protected from light. Do not use cetylpyridinium chloride (CPC) as it is not compatible with MGIT.

The specimen should be processed as soon as possible.

- **Specimen for culture on Lowenstein-Jensen medium (LJ)**

- Specimens that can be cultured in less than 3 days after collection:

Keep refrigerated (2 to 8°C) and protected from light until transport OR immediately transport to the laboratory for processing.

- Specimens that will be cultured more than 3 days after collection:

Use Falcon tubes and add 1% CPC to preserve the specimen for up to 2 weeks. Specimens with CPC should not be refrigerated, as the CPC will crystallize and be ineffective. Samples with CPC can be inoculated on LJ. For inoculation on agar, they require prior neutralization by neutralizing buffer (Difco®).

CPC can be used for specimens tested by Xpert MTB/RIF.

Sputum specimen shipment

To a local laboratory

- Without CPC transport medium: between 2 and 8°C and protected from light;
- With CPC transport medium: should not be refrigerated because at low temperatures the CPC will crystallize and ruin the sample. Specimens should be kept at room temperature, protected from heat and light.

By air to a reference laboratory for culture

Samples are collected and shipped in 50 ml Falcon® conical tubes with screw caps. The tubes are labelled UN 3373, corresponding to Category B infectious substances. If transport times are less than 12 hours, even specimens without CPC can be transported at room temperature.

Samples are triple-packaged, in accordance with IATA packing instruction 650:

1. Primary container holding the sputum sample: tube tightly closed and placed into a latex glove;
2. Secondary container intended to protect the primary container: leak-proof box with enough absorbent material to absorb the entire sample, should the primary container break;
3. Outer packaging intended to protect the secondary container, with UN 3373 labelling.

Information to be provided:

- Primary container: label with the patient's name or identification number and the sample collection date and location;
- Outer package: indicate the name of the receiving laboratory, the complete address (name, street, postal code, locality, country), and telephone number.

All samples must be accompanied by the corresponding laboratory test request form (including clinical information).

Notes:

- Procedures for shipping bacterial strains obtained after culture are different, more complicated, and rarely feasible in practice. Cultures are classified as Category A infectious substances (UN 2814).
- For a detailed description of the shipment procedures, see MSF Medical catalogue, volume 4.

Appendix 8: SOP for lymph node puncture and Xpert MTB/RIF assay⁴

FNAC is used to obtain material from lymph nodes. The material is expressed onto slides and prepared for examination.

Two smears will be prepared with Giemsa stain² to look for caseum, granuloma, giants cells, and epithelioid cells or histocytes and 1 or 2 will be prepared with Ziehl-Neelsen (ZN) stain to look for acid-fast bacilli (AFB).

Equipment

- Needle 23G (in very few cases, it would be possible to use 19G)
- 10 ml syringe
- 2 slides for Giemsa + one or 2 slides for ZN stain
- 10% polyvidone iodine, sterile gauze, gloves

Technique

- Disinfect the area.
- With the needle attached to the syringe, insert the needle deep into the lymph node.
- After the needle has entered the mass, pull back on the syringe plunger to create a vacuum.
- Rapidly move the needle in a to-and-fro fashion to allow material entering the needle.
- When blood or material appears in the needle hub the aspiration should be stopped. Try to aspirate as much as possible of materials, the amount of materials that has been aspirated would have effect on the specificity and sensitivity of diagnosis.
- Release the negative pressure before to take out the needle from the lymph node. Do not continue sucking while taking out the needle, this will avoid aspiration of materiel into the barrel of the syringe and avoid mixing the sample with the possible peripheral blood in the skin.

Appendix 9: SOP for Xpert MTB/RIF assay performance

Xpert MTB/RIF assay is based on hemi-nested real time PCR for simultaneous detection of M. tuberculosis (MTB) and rifampicin (RIF) resistance. The target is the rpoB gene, critical for detection of mutations associated to rifampicin resistance. Xpert MTB/RIF automates all aspects of real time PCR analysis, with results available in 2 hours.




Sample processing

The test can be performed using fresh sputum samples or decontaminated samples prior culture inoculation.

Procedure with fresh sputum samples:

- Ask the patient to rinse the mouth twice before collecting the sample.
- Collect a minimum of 1.5 ml good quality sputum.
- Follow the procedures outlined below:

Procedure for Xpert MTB/RIF*

Step 1	Step 2	Step 3
 <p data-bbox="304 1377 628 1592">Add the reagent 2:1 (v/v) to the sample and shake 10-20 times. Incubate at room temperature for 15 min.; during incubation repeat once shaking for 10- 20 times.</p>	 <p data-bbox="687 1384 1007 1464">With a pipette transfer the diluted sample into a cartridge.</p>	 <p data-bbox="1070 1406 1390 1487">Insert the cartridge in the machine and start the test.</p>

* Source: National Health Laboratory Services, South Africa.

Procedure for sediment samples:

- Sediments can be prepared according to standard decontamination procedure (NALC-NaOH method) and re-suspend with phosphate buffer.
- Ensure 0.5 ml is available for the test; add 1.5 ml of reagent for 0.5 ml of re-suspended sediment.
- Follow the procedure described in the above figure.

Interpretation of the results:

Proper test performance is ensured by 2 internal controls:

- Sample processing control (SPC) ensures adequate processing and monitors presence of inhibition.
- Probe check control (PCC) verifies that the steps of the tests (rehydration, filling of the cartridge, etc.) take place correctly.

When the test is completed the display can show:

- “MTB detected” expressed by levels (the higher the level, the higher the amount of MTB detected in the sample) or “MTB not detected”;
- RIF results expressed as “detected”, “not detected” or “indeterminate” are available only if MTB is detected.

Other possible results:

- Invalid: MTB invalid and SPC failed due to one of several reasons, such as inhibition;
- Error: MTB no result, SPC no result, PCC failed; fail of system components;
- No result: e.g. tests stopped during processing.

Storage of samples and cartridges:

Samples:

- For a period ≤ 3 days: store at 35°C maximum. A cold chain is not required for up to 3 days after collection. During this period of time, overgrowth of normal flora does not have negative influence on the test. However, if a cold chain is available, samples should be stored at 2 to 8°C in order to help their preservation.
- For a period of 4 to 10 days: store refrigerated at 2 to 8°C.

If samples require other testing (i.e. smear microscopy and/or culture), sample storing conditions adequate for microscopy and culture have to be followed. CPC does not interfere with Xpert MTB/RIF testing.

Cartridges:

- To be stored at 2 to 28°C.
- The cartridge should be used within 30 minutes of opening the cartridge lid.
- Cartridges are stable for 7 days after opening the packaging.

Logistic requirements

Power supply

- The device requires stable and uninterrupted power supply.
- Each GeneXpert instrument will need a uninterruptible power supply (UPS).
- The minimum requirement for the functioning of the GeneXpert instrument is to have a 800VA UPS.

Operating temperature

- The operating temperature for GeneXpert instrument device is 15 to 30°C. According to climate conditions, the installation of air conditioning can be recommended to keep the area within the temperature ranges indicated by the manufacturer.

Calibration

- The GeneXpert modules require annual calibration, which must be performed by an authorised service provider or carried out by swapping out the modules. A detailed commercial sales contract and customer support plan should be negotiated with the supplier, guaranteeing regular maintenance, calibration, repair and replacement (when needed).
- Cartridges and reagents shelf-life
- 12 months from date of production.

Storage space

- Each kit contains 10 cartridges and all reagents necessary to run 10 tests. The dimensions of the kit are 27 x 20 x 17 cm and the weight is 800 g.

Lab space

- The GeneXpert IV instrument (4 modules allowing the processing of 4 specimens at the same time) has the following dimensions:
- 29.8 cm wide, 35.6 cm high, 31.1 cm deep; weight: 12 kg. It is designed for indoor use only.
- Provide at least 5 cm of clearance on each side of the instrument to ensure adequate ventilation.
- Do not place the instrument close to the vents of other instruments or air-handling units.

Safety

- The personal protection requirements for microscopy should be adopted, including use of gloves and respirators.

Waste disposal

- Same procedure as for sputum containers. To be noted is the large volume of additional waste generated by Xpert MTB/RIF compared to smear microscopy.

Appendix 10: SOP for the diagnosis of HIV in children

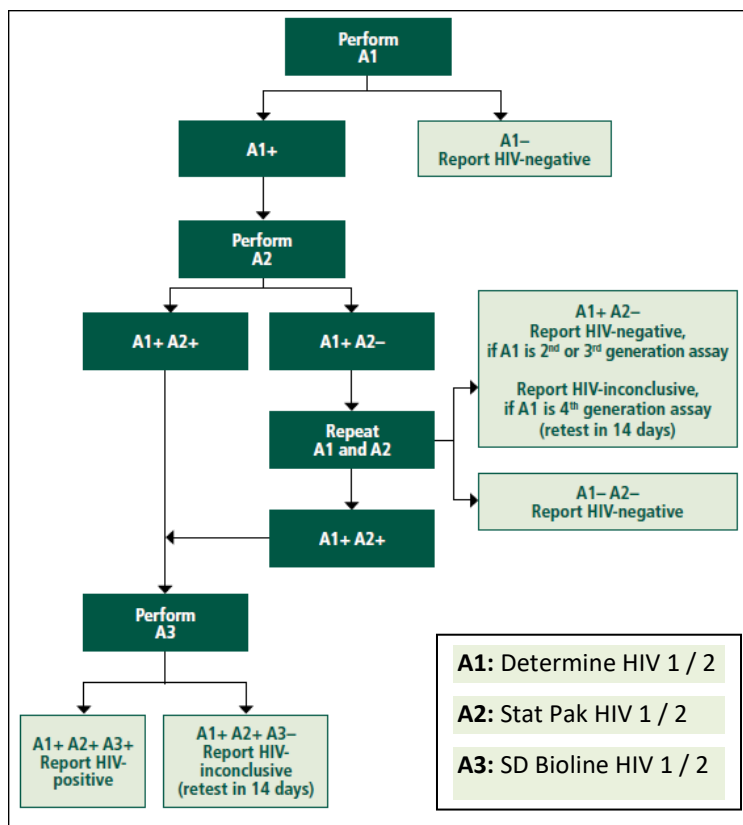
1.1. Indication:

HIV infection should be systematically assessed in all children admitted to the ITFC ward and in children admitted to the Paediatric ward who present with clinical suspicion of HIV infection.

1.2. General principles:

- HIV testing should be performed by trained staff.
- HIV testing can only be performed after counselling and informed consent from the parents.
- In children under 5 years old, the mother will be tested first and the children will be tested only when:
 - Mother is HIV positive
 - Mother is negative but strong suspicion of HIV infection (ie. unsafe blood transfusion, traditional scarification or circumcision) or
 - In the absence of the mother
- HIV testing will be performed by using standard MSF (algorithm 1) or National testing algorithm.
- Children and/or mother with positive HIV diagnosis will be immediately linked to the HIV program, MSF supported or not.

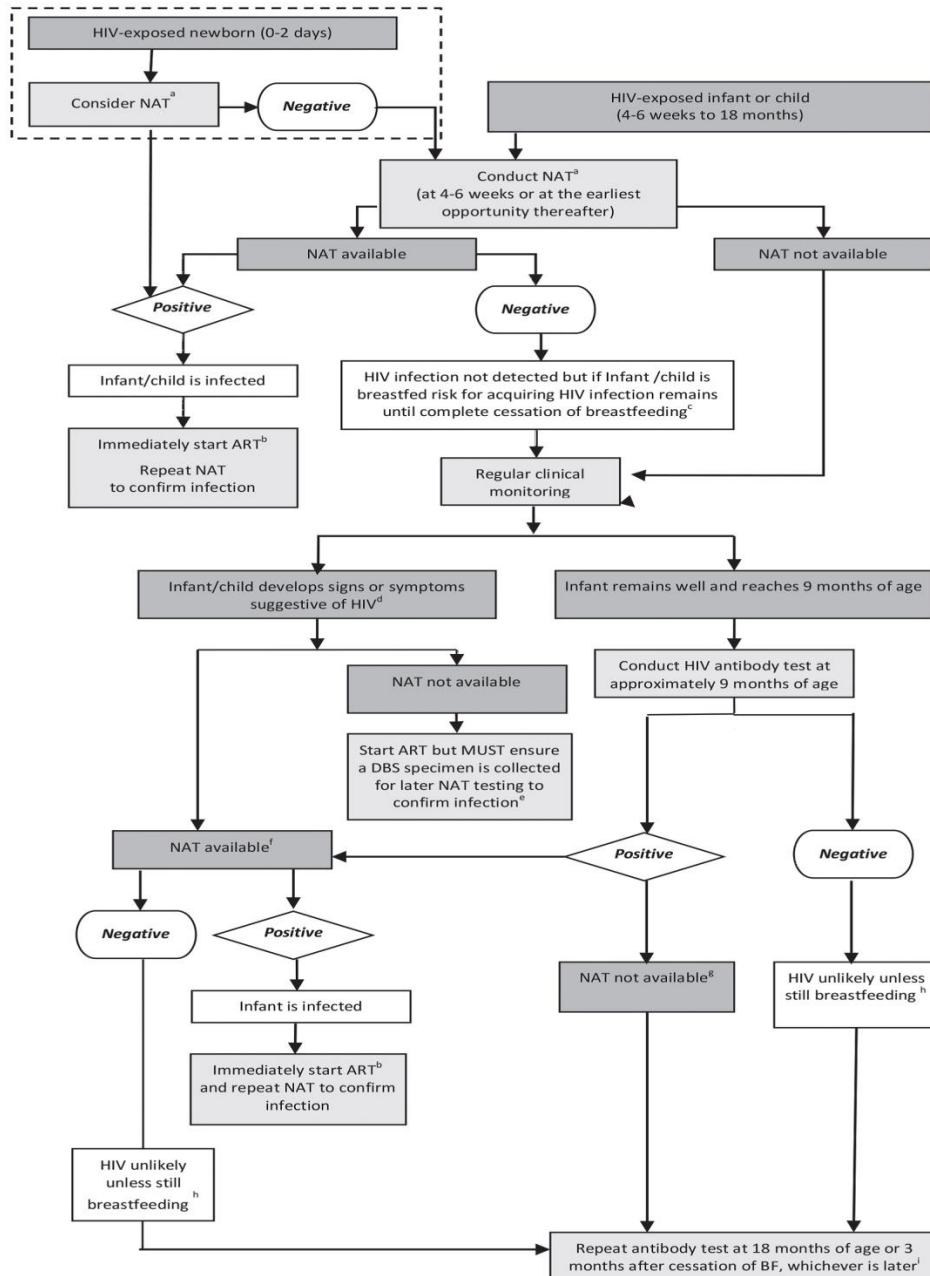
1.3. Algorithm 1: MSF testing algorithm for mothers and children 18 months or more¹



¹ New HIV testing algorithm for MSF setting, October 2017

1.4. MSF testing for children under 18 months:

- If child < 9 months and mother HIV positive or unknown: perform PCR DNA.
- If child is 9 or more months but not yet 18 months, and mother positive or unknown: perform rapid test and confirm with PCR DNA if positive.
- If child is 18 months and not breastfed in the last 6 weeks: follow algorithm 1.



Source WHO guidelines 2016 'Consolidated guidelines on the use of Antiretroviral drugs for treating and preventing HIV infection'

Appendix 11: Checklist for adherence counselling (HIV and TB)

Pre HIV test counselling check list: individual or in group

Reasons and benefits of having an HIV test

What the patient knows about HIV?

What is HIV and its modes of transmission

A brief description of prevention options

Reinforce that results will remain confidential

Reinforce the fact that the patient can deny the test, but explain the importance of doing it

The HIV testing process (finger-prick, testing procedure, timing of results)

The meaning of an HIV-positive and an HIV-negative result

The potential for incorrect results if a person already on ART is given an HIV test

Information regarding the follow-up services that are available in the case of an HIV-positive test result

Assess personal risky behaviour and discuss risk reduction plan

Information about support mechanisms, who will the patient tell about the results? Where can he get support?

Individual testing procedure

Ask for consent for testing

Address any fears related to testing

Post-test individual HIV counselling check list

For NEGATIVE results

Ask the patient if he is ready to receive the results

Give the results simply and clear

Explain the meaning of negative HIV test and the window period and assess if there has been at risk behaviour in the preceding 3 months; recommend re-testing in case of recent exposure

Discuss the importance of remaining negative by educating on methods of prevention (provision of male and female condoms and explain how to use them)

Emphasize on the importance of knowing the HIV status of sexual partner(s) and give information about the availability of partner and couples testing services

For POSITIVE results

Ask the patient if he is ready to receive the results

Give the results simply and clear

Check with open-ended questions that the person understand the meaning of the result

Allow and encourage the patient to ask questions

Let the patient talk about his feelings about the results

Acknowledge the shock of the diagnosis ; offer support

Determine how the patient will get through the next few hours

Discuss eventual disclosure of the results and to whom

Discuss how to protect partner(s) from infection and explain use of condoms

Encourage and offer HIV testing for sexual partners, children and other family members of the client

Provide clear information on ART and its benefits for maintaining health and reducing the risk of HIV transmission, as well as where and how to obtain ART

Encourage and provide time for the client to ask additional questions

Patient education and counselling at screening of TB

Topics

Give emotional support regarding the diagnosis

Assess previous knowledge and explain facts on TB disease

- What is TB (Card 1)
- What are the signs and symptoms of active TB (Card 2)
- What are the ways of transmission and prevention of TB (Card 3)
- What is the relationship between HIV and TB (Card 14)
- What is the difference between drug-sensitive and drug-resistant TB

Assess previous knowledge and explain the facts on TB treatment:

- What does the treatment consist of (Card 5)
- How to adhere (Card 15)
- Side effects of treatment (Card 6)
- Clinic follow-up for DSTB patients
- Clinic follow-up for DSTB patients

Explain risk for family members and ask the patient to bring any family member with TB symptoms and all children < 5 years old

Make a plan on how to adhere to TB treatment (getting ready to start treatment, support system, getting to the clinic, medication schedule, managing missed doses, reminder strategies, storing medication)

When	Patients suspected to have active TB disease, including DR-TB, referred for sputum collection
Mode	In group or individually
Duration	15 minutes

Topics

Explain basic facts on TB (what is TB, signs & symptoms, transmission, prevention, relationship with HIV) (Card 1-2-3)

Explain the procedure of TB diagnosis

Explain how to produce sputum (Card 4)

Patient education and counselling at the start of DSTB treatment

When	Before or at the day of TB treatment initiation
Mode	Individual
Duration	30-45 min

Patient education and counselling after starting DSTB treatment

When	One week after treatment initiation or at the first visit after commencing treatment
Mode	Individual
Duration	30 min

Topics

Give emotional support

Evaluate adherence to TB medication (annex 8) and work around any difficulties taking medication since starting

Review knowledge on TB disease and its treatment

Explain monitoring tests for TB treatment

Explain on use of traditional medication, alcohol and drugs in combination with TB treatment

Remind patient to bring any family member with TB symptoms and all children < 5 years old (if the patient didn't yet)

Patient education and counselling at the end of DSTB intensive phase

When	At the end of DSTB intensive phase
Mode	Individual or in group
Duration	15 min

Topics

Evaluate adherence

Solve any adherence issues

Explain the change in drug regimen for the continuation phase

Explain the need to continue to take treatment throughout the maintenance phase, even if the patient might feel better. Assess and reinforce the patient's motivation to continue treatment

Remind patient to bring any family member with TB symptoms and all children < 5 years old (if the patient didn't yet)

Additional PEC sessions throughout DSTB treatment

When	At any moment of TB treatment if adherence problems are detected
Mode	Individual
Duration	20 min

Topics

Evaluate adherence

Solve any adherence issues

Explain the need to continue to take treatment throughout the treatment, even if the patient might feel better. Assess and reinforce the patient's motivation to continue treatment

Remind patient to bring any family member with TB symptoms and all children < 5 years old (if the patient didn't yet)

Support group TB sessions

When	At any moment of TB treatment if adherence problems are detected
-------------	--

Mode	Group
Duration	45 minutes
Methodology	Discuss challenges and share personal experience without being blamed, judged or stigmatised Can be facilitated by staff member or not Attention to infection control concerns

Appendix 12: Anti-TB dosages for children⁶

Intensive phase

Weight (kg)	Paediatric formulations		Adult formulations		
	HZR 50/150/75	E 100	E 400	H 100	EHZR 275/75/400/150
4	1 tab	1 tab			
5	1 tab	1 tab			
6	1 tab	1 tab			
7	1 tab	1 tab			
8	2 tab	2 tab			
9	2 tab	2 tab			
10	2 tab	2 tab			
11	2 tab	2 tab			
12	3 tab	3 tab			
13	3 tab	3 tab			
14	3 tab	3 tab			
15	3 tab	3 tab			
16	4 tab	–	1 tab		
17	4 tab	–	1 tab		
18	4 tab	–	1 tab		
19	4 tab	–	1 tab		
20	4 tab	–	1 tab		
21	4 tab	–	1 tab		
22	4 tab	–	1 tab		
23	–	–	–	1 tab	2 tab
24	–	–	–	1 tab	2 tab
25	–	–	–	1 tab	2 tab
26	–	–	–	1 tab	2 tab
27	–	–	–	1 tab	2 tab
28	–	–	–	1 tab	2 tab
29	–	–	–	1 tab	2 tab
30-34	–	–	–	–	2 tab
35-39	–	–	–	–	2 ½ tab
40-54	–	–	–	–	3 tab
55-70	–	–	–	–	4 tab
> 70	–	–	–	–	5 tab

⁶ Based on the Appendix 8a of MSF TB Guideline 2014

Continuation phase

Weight (kg)	Paediatric formulation		Adult formulation	
	HR 50/75		HR 75/150	
4	1 tab			
5	1 tab			
6	1 tab			
7	1 tab			
8	2 tab			
9	2 tab			
10	2 tab			
11	2 tab			
12	3 tab			
13	3 tab			
14	3 tab			
15	–		2 tab	
16	–		2 tab	
17	–		2 tab	
18	–		2 tab	
19	–		2 tab	
20	–		2 tab	
21	–		2 tab	
22	–		3 tab	
23	–		3 tab	
24	–		3 tab	
25	–		3 tab	
26	–		3 tab	
27	–		3 tab	
28	–		3 tab	
29	–		3 tab	
30-34	–		2 tab	
35-39	–		2 ½ tab	
40-54	–		3 tab	
55-70	–		4 tab	
> 70	–		5 tab	
	Daily dosing in patients < 30 kg		Daily dosing in patients ≥ 30 kg	
E	15 to 25 mg/kg once daily		15 to 25 mg/kg once daily	
H	7 to 15 mg/kg once daily		4 to 6 mg/kg once daily	
Z	30 to 40 mg/kg once daily		20 to 30 mg/kg once daily	
R	10 to 20 mg/kg once daily		8 to 12 mg/kg once daily	

Appendix 13a: Weight for height in children from 5 to 10 year old

RECONSTRUCTED FROM BMI charts: height between 120,5 and 140,0 cm												
Reconstruction based on WHO 2007 references												
Older children from 60 months to 10 years (110,0 - 140,0 cm)												
MALE		Weight-for-Height (Standing up)					FEMALE					
		-3	-2	-1	Median	cm	Median	-1	-2	-3		
		14.4	15.6	17.0	18.5	110	18.6	17.0	15.5	14.2		
		14.5	15.8	17.1	18.7	110.5	18.8	17.1	15.7	14.4		
		14.6	15.9	17.3	18.9	111	19.0	17.3	15.8	14.5		
		14.8	16.0	17.5	19.1	111.5	19.2	17.5	16.0	14.7		
		14.9	16.2	17.6	19.2	112	19.4	17.7	16.2	14.8		
		15.0	16.3	17.8	19.4	112.5	19.6	17.9	16.3	15.0		
		15.2	16.5	18.0	19.6	113	19.8	18.0	16.5	15.1		
		15.3	16.6	18.1	19.8	113.5	20.0	18.2	16.7	15.3		
		15.4	16.8	18.3	20.0	114	20.2	18.4	16.8	15.4		
		15.6	16.9	18.5	20.2	114.5	20.5	18.6	17.0	15.6		
		15.7	17.1	18.6	20.4	115	20.7	18.8	17.2	15.7		
		15.8	17.2	18.8	20.6	115.5	20.9	19.0	17.3	15.9		
		16.0	17.4	19.0	20.8	116	21.1	19.2	17.5	16.0		
		16.1	17.5	19.2	21.0	116.5	21.3	19.4	17.7	16.2		
		16.2	17.7	19.3	21.2	117	21.5	19.6	17.8	16.3		
		16.4	17.9	19.5	21.4	117.5	21.7	19.8	18.0	16.5		
		16.5	18.0	19.7	21.6	118	22.0	19.9	18.2	16.6		
		16.7	18.2	19.9	21.8	118.5	22.2	20.1	18.4	16.8		
	AGE	16.8	18.3	20.0	22.0	119	22.4	20.3	18.5	16.9	AGE	
	year.month	16.9	18.5	20.2	22.2	119.5	22.6	20.5	18.7	17.1	year.month	
	06:08	17.1	18.6	20.4	22.4	120	22.8	20.7	18.7	17.2	06:10	
	06:09	17.5	19.0	20.6	22.4	120.5	22.8	20.8	18.8	17.3	06:11	
	06:10	17.9	19.2	20.8	22.5	121	22.9	20.9	18.9	17.3	07:00	
	6:11 / 7:00	18.0	19.3	21.0	22.9	121.5	23.0	20.9	19.0	17.4	07:01	
	07:01	18.3	19.6	21.1	23.1	122	23.1	21.0	19.1	17.6	7:02 / 7:03	
	07:02	18.5	19.8	21.3	23.3	122.5	23.3	21.1	19.2	17.7	07:04	
	07:03	18.6	20.0	21.6	23.4	123	23.4	21.2	19.4	17.9	07:05	
	07:04	18.8	20.1	21.8	23.8	123.5	23.6	21.4	19.5	18.0	07:06	
	07:05	18.9	20.3	22.0	24.0	124	23.8	21.5	19.7	18.1	07:07	
	07:06	19.1	20.5	22.2	24.2	124.5	24.2	21.7	19.8	18.3	07:08	
	07:07	19.2	20.6	22.3	24.4	125	24.4	22.0	20.0	18.4	07:09	
	07:08	19.4	20.8	22.5	24.6	125.5	24.6	22.2	20.3	18.7	07:10	
	07:09	19.7	21.1	22.7	24.9	126	24.9	22.4	20.5	18.9	07:11	
	07:10	19.8	21.3	23.0	25.1	126.5	25.1	22.6	20.6	19.0	08:00	
	7:11 / 8:00	20.0	21.5	23.2	25.3	127	25.3	22.7	20.8	19.2	08:01	
	08:01	20.2	21.6	23.4	25.7	127.5	25.5	23.1	21.0	19.3	08:02	
	08:02	20.3	21.8	23.6	25.9	128	25.9	23.3	21.1	19.5	08:03	
	08:03	20.5	22.0	23.8	26.1	128.5	26.1	23.4	21.5	19.6	08:04	
	08:04	20.6	22.3	24.1	26.3	129	26.3	23.6	21.6	20.0	08:05	
	08:05	21.0	22.5	24.3	26.7	129.5	26.7	24.0	21.8	20.1	08:06	
	08:06	21.1	22.6	24.5	26.9	130	26.9	24.2	22.0	20.3	08:07	
	08:07	21.3	22.8	24.7	27.1	130.5	27.1	24.4	22.1	20.4	08:08	
	08:08	21.5	23.0	24.9	27.3	131	27.5	24.5	22.5	20.6	08:09	
	08:09	21.6	23.2	25.2	27.7	131.5	27.7	24.9	22.7	20.9	08:10	
	8:10 / 8:11	21.8	23.5	25.4	27.9	132	28.1	25.1	22.8	21.1	08:11	
	09:00	22.1	23.7	25.6	28.1	132.5	28.3	25.3	23.0	21.2	09:00	
	09:01	22.3	23.9	25.8	28.5	133	28.5	25.6	23.3	21.4	09:01	
	09:02	22.5	24.1	26.2	28.7	133.5	28.9	25.8	23.5	21.6	09:02	
	09:03	22.6	24.2	26.4	28.9	134	29.1	26.0	23.7	21.9	09:03	
	9:04 / 9:05	22.8	24.6	26.6	29.3	134.5	29.5	26.4	23.9	22.1	09:04	
	09:06	23.1	24.8	27.0	29.5	135	29.7	26.6	24.2	22.2	09:05	
	09:07	23.3	25.0	27.2	29.9	135.5	29.9	26.8	24.4	22.4	09:06	
	09:08	23.5	25.2	27.4	30.1	136	30.3	27.2	24.6	22.8	09:07	
	09:09	23.7	25.5	27.6	30.4	136.5	30.6	27.4	25.0	22.9	09:08	
	09:10	23.8	25.7	28.0	30.8	137	31.0	27.6	25.2	23.1	09:09	
	9:11 / 10:00	24.2	25.9	28.2	31.0	137.5	31.2	28.0	25.3	23.3	09:10	
	10:01	24.4	26.3	28.6	31.4	138	31.6	28.2	25.5	23.6	09:11	
	10:02	24.6	26.5	28.8	31.7	138.5	31.8	28.4	25.9	23.8	10:00	
	10:03	24.7	26.7	29.0	32.1	139	32.3	28.8	26.1	24.0	10:01	
	10:04	25.1	26.9	29.2	32.3	139.5	32.5	29.0	26.3	24.1	10:02	
	10:05	25.3	27.2	29.6	32.5	140	32.9	29.4	26.7	24.5	10:03	

Appendix 13b: Weight for height in adolescents

Weight adaptations between 140,0 (BMI charts WHO 2007) to 145,0 cm (NCHS 1982)

Reconstruction based on NCHS-CDC-WHO 1982 references								
Adolescents from 10 to approx 18 years (140,0 - 165,0 cm)								
MALE		Weight-for-Height (Standing up)					FEMALE	
70%	80%	85%	Median	cm	Median	85%	80%	70%
25.1	27.2	29.6	32.5	140	32.9	29.4	26.7	24.5
25.2	27.4	29.7	33.0	140.5	33.2	29.6	26.8	24.7
25.2	27.6	29.9	33.4	141	33.6	29.8	27.0	24.9
25.3	28.0	30.0	33.8	141.5	33.8	30.2	27.4	25.0
25.4	28.2	30.2	34.1	142	34.1	30.4	27.6	25.2
25.4	28.4	30.3	34.7	142.5	34.8	30.7	27.8	25.6
25.5	28.8	30.5	35.0	143	35.6	31.1	28.0	25.7
25.6	29.0	30.6	35.3	143.5	36.0	31.3	28.4	25.8
25.6	29.1	30.8	35.7	144	36.4	31.4	28.6	25.9
25.7	29.2	30.9	36.1	144.5	36.9	31.5	29.1	26.0
25.8	29.2	31.0	36.5	145	37.1	31.5	29.7	26.0
25.8	29.5	31.3	36.8	145.5	37.4	31.8	29.9	26.2
26.0	29.7	31.6	37.2	146	37.8	32.1	30.2	26.5
26.3	30.0	31.9	37.6	146.5	38.1	32.4	30.5	26.7
26.5	30.3	32.2	37.9	147	38.4	32.6	30.7	26.9
26.8	30.6	32.5	38.3	147.5	38.8	33.0	31.0	27.2
27.0	30.9	32.8	38.6	148	39.1	33.2	31.3	27.4
27.3	31.2	33.1	39.0	148.5	39.5	33.6	31.6	27.7
27.5	31.5	33.4	39.3	149	39.8	33.8	31.8	27.9
27.8	31.7	33.7	39.7	149.5	40.1	34.1	32.1	28.1
28.0	32.0	34.0	40.0	150	40.5	34.4	32.4	28.4
28.3	32.3	34.3	40.4	150.5	40.8	34.7	32.6	28.6
28.5	32.6	34.7	40.8	151	41.2	35.0	33.0	28.8
28.8	32.9	34.9	41.1	151.5	41.5	35.3	33.2	29.1
29.1	33.2	35.3	41.5	152	41.9	35.6	33.5	29.3
29.3	33.5	35.6	41.9	152.5	42.3	36.0	33.8	29.6
29.6	33.8	35.9	42.3	153	42.6	36.2	34.1	29.8
29.8	34.1	36.2	42.6	153.5	43.0	36.6	34.4	30.1
30.1	34.4	36.6	43.0	154	43.4	36.9	34.7	30.4
30.4	34.7	36.9	43.4	154.5	43.8	37.2	35.0	30.7
30.7	35.0	37.2	43.8	155	44.2	37.6	35.4	30.9
30.9	35.4	37.6	44.2	155.5	44.6	37.9	35.7	31.2
31.2	35.7	37.9	44.6	156	45.1	38.3	36.1	31.6
31.5	36.0	38.3	45.0	156.5	45.5	38.7	36.4	31.9
31.8	36.3	38.6	45.4	157	46.0	39.1	36.8	32.2
32.1	36.7	38.9	45.8	157.5	46.5	39.5	37.2	32.6
32.4	37.0	39.3	46.2	158	47.0	40.0	37.6	32.9
32.7	37.3	39.6	46.6	158.5	47.6	40.5	38.1	33.3
33.0	37.7	40.0	47.1	159	48.2	41.0	38.6	33.7
33.3	38.0	40.4	47.5	159.5	48.9	41.6	39.1	34.2
33.6	38.4	40.8	48.0	160	49.7	42.2	39.8	34.8
33.9	38.7	41.1	48.4	160.5	50.5	42.9	40.4	35.4
34.2	39.1	41.5	48.8	161	51.6	43.9	41.3	36.1
34.5	39.4	41.9	49.3	161.5	52.8	44.9	42.2	37.0
34.8	39.8	42.3	49.8	162	54.5	46.3	43.6	37.8
35.1	40.2	42.7	50.2	162.5	56.1	47.7	44.9	38.3
35.5	40.5	43.1	50.7	163	56.4	47.9	45.1	38.8
35.8	40.9	43.5	51.1	163.5	56.7	48.2	45.4	39.0
36.1	41.3	43.9	51.6	164	57.0	48.4	45.6	39.5
36.5	41.7	44.3	52.1	164.5	57.3	48.7	45.8	39.8
36.8	42.1	44.7	52.6	165	57.6	48.9	46.0	40.0

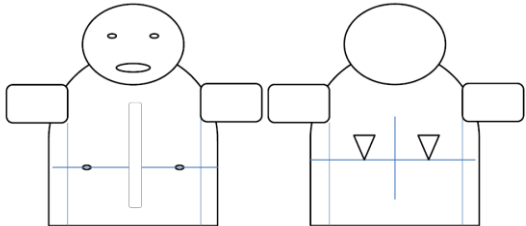
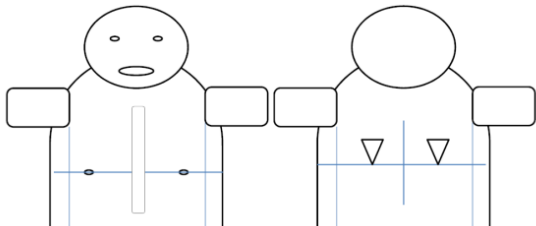
Patient code:

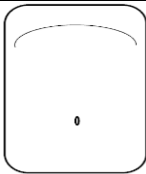
Date of Scan: / /

Baseline [], FU []

Time point: day

Appendix 14: POCUS form

CHEST		
Subpleural nodules	<input type="checkbox"/> normal	<input type="checkbox"/> not evaluable, reason:
	<input type="checkbox"/> pathologic, <input type="checkbox"/> bilateral or <input type="checkbox"/> unilateral	
Consolidation	<input type="checkbox"/> no	<input type="checkbox"/> not evaluable, reason:
	<input type="checkbox"/> yes size: _____ cm	 <p>Location:</p>
Pleural Effusion	<input type="checkbox"/> no	<input type="checkbox"/> not evaluable, reason:
	<input type="checkbox"/> yes size: _____ cm	 <p>Location:</p>
Pericardial effusion	<input type="checkbox"/> no	<input type="checkbox"/> not evaluable, reason:
	<input type="checkbox"/> yes	
Other findings chest:		

ABDOMEN		
Ascites	<input type="checkbox"/> no	<input type="checkbox"/> not evaluable, reason:
	<input type="checkbox"/> yes	 <p>Location:</p>
Focal liver lesions (hypoechoic)	<input type="checkbox"/> no	<input type="checkbox"/> not evaluable, reason:
	<input type="checkbox"/> yes	
Focal splenic lesions (hypoechoic)	<input type="checkbox"/> no	<input type="checkbox"/> not evaluable, reason:
	<input type="checkbox"/> yes	
Abdominal lymph nodes (> 1cm short axis)	epigastric	<input type="checkbox"/> no <input type="checkbox"/> not evaluable, reason:
		<input type="checkbox"/> yes
	splenic hilar	<input type="checkbox"/> no <input type="checkbox"/> not evaluable, reason:
		<input type="checkbox"/> yes
	Mesenteric/paraaortal	<input type="checkbox"/> no <input type="checkbox"/> not evaluable, reason:
		<input type="checkbox"/> yes
Other findings abdomen:		

Interpretation: POCUS positive **high** suspicion / **low** suspicion; POCUS negative **no** suspicion
 FU at 2 months: Resolution of signs Improvement of signs No change in signs
 Compliance of patient: **good**, **moderate**, **bad**
 Duration of POCUS: < 10 min, 10-20 min, 20-30 min, > 30 min
 Impact in decision: no change change repeat POCUS

