# PHARMACOKINETICS OF DRUGS USED TO TREAT DRUG SENSITIVE-TUBERCULOSIS IN BREASTFEEDING MOTHER-INFANT PAIRS:

## AN OBSERVATIONAL PHARMACOKINETIC STUDY

| | |
|---|---|
| **Area:** | Active-TB |
| **Type:** | Observational |

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**Document History**

| Document | Version Date | Summary of Changes |
|---|---|---|
| Original protocol | 27 OCT 2021 | N/A |
| Pre-ethics version | 27 OCT 2021 | N/A |
| Response to initial IDI REC, V 2.0 | 23 NOV 2021 | Clarifications as required by IRB. Added exclusion that breastfed infants should not be aged over 12 months. |
| Clarification from Sponsor | 23 NOV 2021 | Clarification on safety reporting (DAIDS criteria to be used) |
| Minor amendment, 3.0 | 14 APR 2022 | Provision for participants to return for a second PK visit in the continuation phase of TB treatment if they are first sampled during the intensive phase of TB treatment<br><br>Minor clarifications |

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# PROTOCOL SUMMARY

| | | |
|---|---|---|
| | **Hypothesis** | Active tuberculosis drug exposure to the breastfed infant may be clinically important. |
| | **Aim** | To define transfer of Isoniazid, Rifampicin, Pyrazinamide and Ethambutol to the breastfed infant.<br><br>To determine the area under the concentration-time curve (AUC), clearance and volume of distribution of these drugs. |
| | **Rationale** | Existing data on anti-TB drug penetration into breastmilk is very sparse and information on clinically relevant infant exposure to anti-TB drugs is even more limited. This is an important knowledge gap both for safety, and because therapeutic concentrations could be 1) protective in exposed infants, obviating the need for TB preventive therapy or 2) sub- therapeutic concentrations could select for resistance in those infants infected with *Mycobacterium tuberculosis*. |
| | **Study design** | Observational pharmacokinetic study |
| | **Inclusions** | 1. A personally signed and dated informed consent document indicating that the participant has been informed of all pertinent aspects of the study.<br><br>2. Participants who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.<br><br>3. Woman is aged 18 years or older<br>4. Receiving treatment for active TB<br>5. Pregnant or breastfeeding at enrolment |
| | **Exclusions** | • Severe maternal or infant illness which in the opinion of the patient's clinician would interfere with her participation in the study<br>• Breastfed infant is aged over 12 months |
| | **Primary Endpoints** | 1) Concentrations of anti-TB drugs in maternal plasma and breastmilk at 0, 2, 4, 6, 8 and, in some cases, 24-hours post-dose<br><br>2) Concentrations of anti-TB drugs in infant bloodat maternal pre-dose, and up to 8 hours post maternal dose.<br><br>3) Area under the concentration-time curve (AUC) of anti-TB drugs in maternal plasma and breastmilk |

| | | |
|---|---|---|
| | | 4) Breast milk to maternal plasma (M:P) ratio of TB drugs |
| | **Secondary Endpoints** | 1. Maximum concentration (Cmax) and time to maximum concentration (Tmax) of the TB drugs in maternal plasma and breastmilk<br>2. Infant development (using Gross Motor Development Score)<br>3. Depression and anxiety assessments for breastfeeding mothers |
| | **Secondary Objectives** | 1) To describe covariates influencing drug exposure in maternal plasma, breast milk and infant plasma<br>2) To develop a population pharmacokinetic model including the breast and the infant as compartments, which will both enable optimal use of sparse data from future studies, and also enable simulations of different doses or combinations.<br>3) To assess depression and anxiety levels among breastfeeding mothers on first line anti-TB drugs.<br>4) Beliefs about medicines in breastfeeding mothers receiving TB treatment |
| | **Number recruited** | 20 mother-infant pairs |
| | **Approximate timelines** | Study to commence as soon as approvals in place.<br>Recruitment estimated to take two years.<br>End of study on completion of analysis. |

**List of Abbreviations**

| | |
|---|---|
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| AUC | Area under the concentration-time curve |
| BMQ | Beliefs and Medicines Questionnaire |
| Cmax | Maximum concentration |
| CRF | Case report form |
| DBS | Dried blood spot |
| FDA | United states food and drug administration |
| GAD | Generalised Anxiety Disorder |
| HCT | Haematocrit |
| HIV | Human immunodeficiency virus |
| IDI | Infectious Diseases Institute |
| M:P ratio | Milk to Plasma ratio |
| PK | Pharmacokinetic |
| PHQ | Patient Health Questionnaire |
| TB | Tuberculosis |
| Tmax | Time to maximum concentration |
| WHO | World Health Organisation |

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# INTRODUCTION

## 1.1. Background

Worldwide, ~50% of women take medication during breastfeeding(1). Data surrounding the exposure of the breastfed infant to drugs and any associated risks are sparse (2). Despite longstanding recommendations from the US Food and Drug Administration (FDA) for lactation studies to be performed close to licensing for drugs anticipated to be widely used in women of childbearing age (3), such studies are rarely undertaken. Drugs taken by the breast feeding mother on TB treatment can be passed from the maternal circulation to her milk and then to the breastfed infant, a concern of effects of anti-tuberculosis drugs on nursing infants (4). Most TB drugs are metabolized by the liver, triggering a potential risk of drug accumulation in infants due to their immature liver function particularly in premature infants (5), (6).

Drugs are transferred to milk in small quantities, and many have been used without obvious infant toxicity for many years hence the large gaps in the data. Pharmacokinetic (PK) information of anti- TB drugs transfer to breast milk and breastfed infant is crucial to limit the development of drug resistance and understand the safety of prolonged exposure through breast milk.

## 1.2. Problem Statement

Whilst data on TB drug penetration into breastmilk is limited, information on clinically relevant infant exposure to TB drug-sensitive is even more limited and is an important knowledge gap both for safety, and because therapeutic concentrations could be 1) protective in exposed infants, obviating the need for TB preventive therapy or 2) sub-therapeutic concentrations could select for resistance in those infants infected with Mycobacterium tuberculosis.

## 1.3. Disease Setting/Patient Population

Breastfeeding women, including those living with HIV, treated for TB will be recruited prospectively from Infectious Diseases clinic (IDI) and IDI Kampala City Council Authority (KCCA) affiliated clinics. The clinics treat pregnant and breast-feeding women infected with TB. We anticipate that 80% of women will be living with HIV. Drug-drug interactions between antiretroviral therapy (ART) and TB drugs could affect the exposure of TB drugs. Data on concomitant medication will be recorded and included as a covariate in the pharmacokinetic analysis. In accordance with national protocol, the infants of mothers diagnosed with TB treatment will receive isoniazid preventive therapy for six months (the duration of the mothers' TB treatment).

# 2. STUDY OBJECTIVES AND ENDPOINTS

## 2.1. Objectives

To define transfer of isoniazid, Rifampicin, Pyrazinamide and Ethambutol to the breastfed infant.

To determine the AUC, clearance and volume of distribution of these drugs.

**Primary Endpoints**

1. Concentrations of TB drugs in maternal plasma and breastmilk at 0, 2, 4, 6, 8 and, in some cases, 24-hours post-dose

2. Concentrations of drugs in infant blood at maternal pre-dose, and up to 8 hours post maternal dose.

3. Area under the concentration-time curve (AUC) of TB drugs in maternal plasma and breastmilk

4. Breast milk to maternal plasma (M:P) ratio of TB drugs

**Secondary endpoints**

1. Maximum concentration (Cmax) and time to maximum concentration (Tmax) of the TB drugs in maternal plasma and breastmilk

2. Infant development (using Gross Motor Development Score)

3. Depression and anxiety assessments for breastfeeding mothers

4. Beliefs about medicines in breastfeeding mothers receiving TB treatment

## 3. STUDY DESIGN

Pregnant or lactating women requiring treatment for drug sensitive-TB will be identified and invited for sampling. If they are pregnant when identified, they will be invited for sampling after delivery. Plasma and breastmilk samples will be obtained pre-dose and at 2, 4, 6, and 8 hours post-dose. If logistics permit (for example living close to the research unit), she will be invited for a further sample at 24 hours post-dose. A heelprick sample will also be obtained from their breastfed infants at maternal trough (prior to maternal dose) and at a random timepoint (once per infant) over the 8-hour pharmacokinetic sampling visit in order to characterize concentrations of these drugs over an 8-hour dosing interval. We will determine concentrations of total plasma and breastmilk Isoniazid, Rifampicin, Pyrazinamide and Ethambutol.

If a participant has her first pharmacokinetic profile in the intensive phase of TB treatment (whilst on all four of isoniazid, rifampicin, pyrazinamide and ethambutol), she will be invited for a subsequent sampling day with the same time points when she is on the continuation phase of therapy (rifampicin and isoniazid).

## 4. PARTICIPANT SELECTION

### 4.1. Inclusion Criteria

Participants must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. A personally signed and dated informed consent document indicating that the participant has been informed of all pertinent aspects of the study.
2. Participants who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
3. Woman is aged 18 years or older
4. Receiving treatment for drug sensitive TB
5. Pregnant or breastfeeding at enrolment

### 4.2. Exclusion Criteria

Participants presenting with any of the following will not be included in the study:

- Severe maternal or infant illness which in the opinion of the patient's clinician would interfere with her participation in the study.
- Breastfed infant is aged over 12 months

## 5. TREATMENTS OF PARTICIPANTS

This is an observational study whereby no changes will be made to the administered medication.

### 5.1. Allocation to Treatment/Group

Not applicable

### 5.2. Drug Supplies

All women (and infants) will continue to receive their TB treatment as prescribed by the clinic where they receive clinical care.

#### 5.2.1. Drug Storage and Drug Accountability

Drug will be stored and dispensed from the hospital pharmacy, with no special procedures relating to this observational protocol.

### 5.3. Concomitant Medication(s)

At every study visit, women will be asked about concomitant medication and the results noted on the case report from (CRF).

# 6. STUDY PROCEDURES

## 6.1. Informed Consent

Women will be identified as they attend the clinic for TB treatment at the IDI and KCCA clinics Hospital in Uganda. Should a woman express willingness to participate, once her eligibility for enrolment in the study has been determined, informed consent will be obtained.

Each potentially eligible participant must sign an Informed Consent Form prior to the conduct of any screening procedures. Participants will be given the opportunity to ask any questions regarding the trial at this stage. Screening evaluations will be used to determine the eligibility of each candidate for study enrolment.

*If the participant is unable to read and/or write, an impartial witness should be present during the informed consent discussion. The witness should be able to read the consent form and participant information leaflet in the participant's chosen language. After the written informed consent form is read and explained to the participant, and after they have orally consented to their participation in the study, and have either signed the consent form or provided their fingerprint, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the patient and that informed consent was freely given by the patient.*

## 6.2. Screening

At the screening visit, the participant will be evaluated against the eligibility criteria. Some women who intend to breastfeed will be identified in late pregnancy but will still be on TB treatment during breastfeeding. In this situation, consent will be sought, and details of how to contact her will be recorded with the aim to bring her for the pharmacokinetic sampling detailed in Section 6.3.2 at approximately 6 weeks postpartum. The exception to this will be where a mother will change from the four-drug intensive to the two-drug continuation phase of TB treatment prior to 6 weeks postpartum, in which case attempts to schedule the sampling visit whilst still on the intensive phase will be made.

The study is being performed because there are no clear data that describe how much drug transfers from mother to breastfed infant. As this is an observational study, it has already been decided by the treating clinician that the mother requires the medication for her health and that benefits outweigh risks. Exclusive breastfeeding complies with WHO guidelines. There are no specific harms relating to the TB treatment about which we should specifically inform the mother prior to participation in the study, but rather the study aims to increase understanding.

## 6.3. Study Period

### 6.3.1. Enrolment

At enrolment, the mother will be assessed clinically.

### 6.3.2. Pharmacokinetic Study Day

On arrival, an intravenous cannula will be inserted into her antecubital fossa, and samples taken for trough drug measurement. After a standardized breakfast she will be administered her medication. Blood samples will be collected at 2, 4, 6, 8 and ideally* 24 hours. She will be advised to freely breastfeed her baby. She will be asked to provide a 2-5 ml sample of expressed breast milk pre-dose, and at 2, 4, 6 and 8 hours post dosing. A blood sample from the infant will be collected at maternal trough (pre-dose) and at a 3-8 hours post maternal dose (the second time point will be allocated sequentially to ensure spread of datapoints). The mother will be administered a standard lunch.

*Due to the logistic considerations of sampling a postpartum mother and her infant who may have travelled a long distance to the clinic, the 24-hour sample may not be collected in all cases.

Maternal albumin and creatinine will be sampled as they are important for isoniazid exposure. Maternal questionnaires will be filled on each visit to assess depression and anxiety; Generalised anxiety disorder questionnaire (GAD-7), Patient health questionnaire (PHQ-9), and the Beliefs about medicines questionnaire (BMQ). Infant clinical assessment will include use of the Gross Motor Development (GMD) checklist, see appendix.

| | | Study Period (8h)^, time relative to maternal dose | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Subject | Study Procedure | On arrival | 0h | 2h | 4h | 6h | 8h | 24h^ |
| Mother | Confirm willingness to proceed | x | | | | | | |
| | Clinical assessment | x | | | | | | |
| | BMI | x | | | | | | |
| | Blood for creatinine and albumin | | | x | | | | |
| | Blood PK sample | x | | x | x | x | x | x |
| | BM PK sample | x | | x | x | x | x | x |
| | Standard meal | | x | | | x | | |
| | Observed dosing | | x | | | | | |
| | PHQ9, GAD7 and BMQ questionnaires | | | | X~ | | | |
| Infant | Clinical assessment | x | | | | | | |
| | Weight | x | | | | | | |
| | PK sample | x | | | | x* | | |
| | *Time of second infant DBS to be recorded, between 3 and 8h | | | | | | | |
| | ^Due to logistic constraints, the 24 hour may not be collected in every participant | | | | | | | |
| | ~can be any time during PK day | | | | | | | |

## 6.4. End of TB treatment outcomes

End of TB treatment outcomes (cured, treatment completed, died, defaulted or transferred out) will be collected from the TB registry.

### 6.5. Participant Withdrawal

Participants may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the participant to comply with the protocol required schedule of study visits or procedures.

If a participant does not return for a scheduled visit (for example, has given consent but then does not return for the pharmacokinetic sampling day detailed in 6.3.2), every effort should be made to contact the participant. *On enrolment participants will have been asked to provide contact numbers and directions to their home. Initial attempts will be made to speak to the participant by telephone, ascertaining the reasons for not attending clinic.* In any circumstance, every effort should be made to document participant outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the participant regarding any unresolved adverse events (AEs).

If the participant withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected.

## 7. ASSESSMENTS

### 7.1. Safety

Given that this is an observational study, we do not have concerns about the safety of the medication received. However, we will appropriately record and respond to adverse events related to the study procedures. These events might include adverse events relating to sampling of maternal blood, breastmilk or infant blood; these will be detailed on the case report form, and the participant followed until the event has resolved. Any events that do occur will be listed and analysed according to DAIDS criteria. Given that this is not a clinical trial, and the medication used is not an investigational product, there is no formal requirement for notification of adverse events to the regulatory authorities.

The potential risk to healthcare workers is not considered higher than routine clinical work in this environment, where incidence and prevalence of HIV and TB are both high. Appropriate universal precautions will be taken.

### 7.2. Pharmacokinetics Assessments

#### 7.2.1. Blood for pharmacokinetic analysis

All efforts will be made to obtain the pharmacokinetic samples at the scheduled nominal time relative to dosing. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of clinical investigators

#### 7.2.2. Sample Handling

Maternal plasma and breast milk will initially be processed and stored in a -80°Celsius freezer at IDI core laboratory.

Drug concentrations will be determined in plasma, infant DBS and total breastmilk using liquid chromatography-tandem mass spectrometry.

### 7.2.3. Justification for PK/other sample shipment

This protocol aims to contribute to bioanalytical capacity in Uganda and all methods will be developed and performed at IDI. No shipment is therefore necessary.

## 8. DATA ANALYSIS/STATISTICAL METHODS

### 8.1. Sample Size Determination

This study is exploratory, as no prior study has characterized the exposure of these drugs in maternal plasma, breastmilk and infant plasma. There are no prior data upon which to build a sample size calculation, and there is no comparison between groups which requires statistical analysis with a pre-specified certainty.

Since no information is available about the penetration of these drugs into breastmilk, we used the following approach, described in detail for rifampicin.

We modified a previously published pop-PK model of rifampicin in plasma, adding a compartment to describe breastmilk concentrations. This was characterised using an approach similar to an effect compartment (7) described by a time delay and an accumulation ratio between breastmilk and plasma. The half-life of the delay was fixed to 1 h and the accumulation ratio to 1.5, with 30% between-subject variability in both parameters. These were chosen to mimic a PK profile similar to Waitt et al (8). We assumed 15 individuals (considering a mother-infant dyad as a single unit) with an intensive PK sampling at 0, 1, 2, 4, 6 and 8 hours post-dose of paired plasma and breastmilk (30% error in the breastmilk measurements was assumed) and performed Stochastic Simulations and Estimations (SSEs) (9) to evaluate trial design. Our design can characterise all the typical values of the plasma PK parameters with precision of better than 11% RSE, and all the breastmilk parameters are well characterised with a precision of 1.14% and 0.591% RSE on delay and accumulation ratio, respectively.

Interim analysis after five participants is part of study design

### 8.2. Analysis of Endpoints

Pharmacokinetic data will be analysed using a population pharmacokinetic approach to estimate pharmacokinetic parameters and produce modelled fits to exposure data (10, 11) Inter-individual variability will be quantified in relation to the covariates.

Non-compartmental methods will be used to assess correlations between maternal breast milk drug concentrations and measures of drug exposure in the infant (eg AUC) and pharmacodynamic factors.

### 8.2.1. Analysis of Primary Endpoint

#### 8.2.1.1. Non-Compartmental Analysis

Plasma pharmacokinetic parameters including the maximum plasma concentration ($C_{max}$), time to maximum plasma concentration ($T_{max}$), and area under the plasma concentration versus time curve ($AUC_{last}$, $AUC_{\tau}$) for (drugs) will be estimated using non-compartmental analysis. If data permit or if considered appropriate, area under the plasma concentration versus time curve to infinity ($AUC_{inf}$), terminal elimination half-life ($t_{1/2}$), plasma clearance (CL or CL/F), apparent volume of distribution ($V_d$ or $V_d$/F) will be also estimated, as data allow. The single dose and/or steady-state PK parameters will be summarized descriptively by dose, cycle and day.

#### 8.2.1.2. Population Pharmacokinetic (pop-PK) analysis

The population pharmacokinetic models will be applied to evaluate whether the drug concentrations are consistent with the expected exposures reported previously. If discrepancies between the observed exposure and the model-expected levels are observed, the models will be adjusted by re-estimating the values of the pharmacokinetic parameter values, with the use of Bayesian priors.

Drug concentrations in breastmilk will be incorporated in the maternal population pharmacokinetic models using an effect compartment strategy, which will allow accurate estimation of the accumulation in breastmilk compared to plasma. Exposure to isoniazid and rifampicin in breastfed infants will be compared with the range of concentrations achieved in adults given therapeutic doses, assuming a minimal duration of exposure from delivery and a maximal duration from the time the mother started the drug (to account for placental transfer)

### 8.3. Safety Analysis

Safety events relating to the study procedures will be graded and analyzed.

### 8.4. Interim Analysis

Not applicable

### 8.5. Data Safety and Monitoring Committee

Not applicable

## 9. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct periodic monitoring may be conducted to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. Additionally, the study site may be participant to review by the Institutional Review Board (IRB) and/or to inspection by appropriate regulatory authorities.

# 10. DATA HANDLING/RECORD RETENTION

## 10.1. Case Report Forms (CRF)

A CRF is required and should be completed for each included participant.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

## 10.2. Record Retention and Archiving

To enable evaluations and/or audits, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and clinic records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports).

Investigator records must be kept for as long as required by applicable local regulations (10 years in Uganda). When more than one requirement can be applied, records must be maintained for the longest period provided.

## 10.3. Confidentiality

Clinical data will be entered into a study specific database by designated staff on a regular basis from completed Case Record Forms (CRF). Case Record Forms and other source documents will be kept in locked cabinets. Data will be entered on a regular basis to ensure that it is up to date. The database will be entered on regular basis on a secure PC, as will the pharmacokinetic data that will be received by the laboratories. Access to database will be given to authorized personnel only (members of the immediate study team) and a log of authorized personnel will be stored in the trial master file. CRF and trial documents will be kept in locked cabinets. No participant identifying information will be disclosed in any publication or at any conference activities arising from the study.

## 10.4 Insurance

This observational study will be covered under the University of Liverpool's existing policy with Newline Insurance.

# 11. ETHICS

## 11.1. Institutional Review Board (IRB)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents from the IRB. All correspondence with the IRB should be retained in the regulatory or trial master file. Copies of IRB approvals should be filed with other study documents.

## 11.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Participants and the Declaration of Helsinki.

In addition, the study will be conducted in accordance with the protocol, GCP guidelines, and applicable local regulatory requirements and laws.

## 11.3. Participant Information and Consent

All parties will ensure protection of participant personal data and will not include participant names on any forms, reports, publications, or in any other disclosures, except where required by laws.

The informed consent document used in this study, and any changes made during the course of the study, must be prospectively approved by the IRB.

The investigator, or a person designated by the investigator, will obtain written informed consent from each participant or the participant's legal representative before any study-specific activity is performed. The investigator will retain the original of each participant's signed consent document.

# 12. DEFINITION OF END OF STUDY

*The study will be considered complete when the target number of participants has been enrolled, and have completed the study period and the data analysis is complete.*

# 13. PUBLICATION AND DISSEMINATION OF STUDY RESULTS

Study findings will be disseminated to researchers at scientific conferences and peer-reviewed infectious disease and pharmacology journals. Specifically, for Uganda, study results will be communicated to the National Tuberculosis and Leprosy programme in the National Department of Health through meetings and reports. The Community Engagement Plan will detail the engagement with communities at all stages of the protocol from inception through dissemination, and activities under the related Wellcome Public Engagement Enrichment award Attaining Equity of Access to Research (At The EQUATOR) will ensure meaningful two-way dialogue throughout.

Specifically, through At The EQUATOR, the following activities are proposed with regard to the MILK protocols:

**During Study Set-Up**

Early consultation with CAB to determine which community members to approach for dialogue

Initial community meeting with religious leaders, women' s local representative and community members, involving oral discussion and written flyers with pictures and simplified, translated text.

Identification of key community members who are interested in co-creation of materials and resources.

Establishment of social media channels relating to study activities.

Engagement with journalists/ media – identify interested parties.

**At Site Initiation**

Community meeting at site for Q&A and more specific information about recruitment

Radio broadcast or presentation of drama and song relating to activities.

Tailor-made flyers and posters including photos with key, simplified text

**During Study**

Community meetings every 1-2 months for updates on study progress

Social media updates

Media updates

**At Dissemination**

Dissemination meeting/ event

Listen to priorities about ongoing research, start to consider future work

## 14. FUNDING

This study is funded by a Wellcome Trust Clinical Research Career Development Fellowship awarded to Catriona Waitt.

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# 15. APPENDIX 1: INFANT GROSS MOTOR DEVELOPMENT SCORE

Study ID of child:_____

**Examination of the baby/child at the time of PK visit**

| | | I[st] examination |
|---|---|---|
| | | Date: |
| | Name of examining doctor or nurse | |
| 1 | Age of child (in months) | |
| 2 | Weight (kgs) | |
| 3 | Length of child (cm)? | |
| 4 | Head circumference (cm)? | |
| 5 | Middle Upper Arm Circumference (cm)? | |
| 7 | Is the child well at the moment? (Yes/ **No**)* | |
| 8 | Is the baby/child picking up weight as he/she should?<br>(Normal trajectory/ **staying the same weight/losing weight**)* | |
| 9 | Any congenital abnormalities identified postnatally? (**Yes**/No)* | |
| 16 | Is the baby being breast-fed or bottle-fed, or both? | |
| 17 | If the baby is breast-fed, is milk from a donor used or partly used? | |

***** If the answer for any of these questions is the red option provide details on the last page of this assessment form.

**Development of the baby/child:**

| | **Examination date:** |
|---|---|
| Age of child (in months) | |
| Turn his head to hear your voice? | |
| Recognise his caregiver? (Smile) | |
| Sits with support | |
| Laughs and squeals | |
| Explores objects | |
| Sits unsupported | |
| Rolls both ways | |
| Babbles | |
| Stranger anxiety | |
| Gets from sitting into crawling or kneeling | |
| Says ‘mama’, ‘dada’ | |
| Gestures ‘bye bye’ | |
| Walks | |
| Responds to own name | |
| Points at wanted objects | |

## Details for questions on page 1 of this assessment form or any other details on the child

| Question no | Details |
|---|---|
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## List of drugs the baby has been on since birth

| Name of drug | Dosage | Date started | Drug stopped |
|---|---|---|---|
| | | | |
| | | | |
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## 16. APPENDIX 2: PHQ-9 AND GAD-7 TOOL

### Patient Health Questionnaire and General Anxiety Disorder (PHQ-9 and GAD-7)

Date_____ Patient ID: _____ Date of Birth: _____

***Over the last 2 weeks, how often have you been bothered by any of the following problems? Please circle your answers.***

| ***PHQ-9*** | **Not at all** | **Several days** | **More than half the days** | **Nearly every day** |
|---|---|---|---|---|
| 1. Little interest or pleasure in doing things. | 0 | 1 | 2 | 3 |
| 2. Feeling down, depressed, or hopeless. | 0 | 1 | 2 | 3 |
| 3. Trouble falling or staying asleep, or sleeping too much. | 0 | 1 | 2 | 3 |
| 4. Feeling tired or having little energy. | 0 | 1 | 2 | 3 |
| 5. Poor appetite or overeating. | 0 | 1 | 2 | 3 |
| 6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down. | 0 | 1 | 2 | 3 |
| 7. Trouble concentrating on things, such as reading the newspaper or watching television. | 0 | 1 | 2 | 3 |
| 8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual. | 0 | 1 | 2 | 3 |
| 9. Thoughts that you would be better off dead, or of hurting yourself in some way. | 0 | 1 | 2 | 3 |
| ***Add the score for each column*** | | | | |

**Total Score (add your column scores): _____**

**Depression severity:0-4 None, 5-9 Mild, 10-14 Moderate, 15-19 Moderately severe, 20-27 Severe**

If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people? (Circle one)

**Not difficult at all Somewhat difficult Very Difficult Extremely Difficult**

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***Over the last 2 weeks, how often have you been bothered by any of the following problems? Please circle your answers.***

| ***GAD-7*** | **Not at all sure** | **Several days** | **Over half the days** | **Nearly every day** |
|---|---|---|---|---|
| 1. Feeling nervous, anxious, or on edge. | 0 | 1 | 2 | 3 |
| 2. Not being able to stop or control worrying. | 0 | 1 | 2 | 3 |
| 3. Worrying too much about different things. | 0 | 1 | 2 | 3 |
| 4. Trouble relaxing. | 0 | 1 | 2 | 3 |
| 5. Being so restless that it's hard to sit still. | 0 | 1 | 2 | 3 |

| | | | | |
|---|---|---|---|---|
| 6. Becoming easily annoyed or irritable. | 0 | 1 | 2 | 3 |
| 7. Feeling afraid as if something awful might happen. | 0 | 1 | 2 | 3 |
| ***Add the score for each column*** | | | | |

**Total Score (add your column scores): _____**

If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people? (Circle one)

**Not difficult at all** **Somewhat difficult** **Very Difficult** **Extremely Difficult**

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# 17. APPENDIX 3: BELIEFS ABOUT MEDICINES QUESTIONAIRE

## Questions relating to medicine use in general

This section explores your views and concerns (if any) about taking medicines in general.

Please answer every question by ticking the box that best describes your views to each statement.

Please remember, there are no "right" answers to the questions, we are simply interested in your views.

| | | Strongly agree | Agree | Uncertain | Disagree | Strongly disagree |
|---|---|---|---|---|---|---|
| G1 | Doctors use too many medicines | | | | | |
| G2 | Patients who take medicines should stop their treatment for a while every now and again | | | | | |
| G3 | Most medicines are addictive | | | | | |
| G4 | Natural remedies are safer than medicines | | | | | |
| G5 | Medicines do more harm than good | | | | | |
| G6 | All medicines are poisons | | | | | |
| G7 | Doctors place too much trust on medicines | | | | | |
| G8 | If doctors had more time with patients they would prescribe fewer medicines | | | | | |

**Specific questions relating to TB TREATMENT**

The following questions explore your views and concerns (if any) around taking TB treatment specifically.

Please answer every question by ticking the box that best describes your views to each statement.

Please remember, there are no "right" answers to the questions, we are simply interested in your views.

| | | Strongly agree | Agree | Uncertain | Disagree | Strongly disagree |
|---|---|---|---|---|---|---|
| S1 | My health at present depends on TB treatment | | | | | |
| S2 | Having to take TB treatment worries me | | | | | |
| S3 | My life would be impossible without TB treatment | | | | | |
| S4 | Without TB treatment I would be very ill | | | | | |
| S5 | I sometimes worry about the long term effects of TB treatment | | | | | |
| S6 | The TB treatment is a mystery to me | | | | | |
| S7 | My health in the future depends on TB treatment | | | | | |
| S8 | The TB treatment disrupts my life | | | | | |
| S9 | I sometimes worry about becoming too dependent on TB treatment | | | | | |
| S10 | TB treatment protects me from becoming worse | | | | | |