QUALITY CONTROL MANUAL

MYCOBACTERIOLOGY – LABORATORIES

GLOBAL

Protocol Title: A Phase 3, Open-Label Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of the Combination of Moxifloxacin plus PA-824 plus Pyrazinamide after 4 and 6 months in Adult Subjects with Drug-Sensitive Smear-Positive Pulmonary Tuberculosis and after 6 months of Treatment in Adult Subjects with Multi-Drug Resistant, Smear Positive Pulmonary Tuberculosis.

Protocol Number: NC-006-(M-Pa-Z)
Protocol Name: STAND (Shortening **T**reatments by **A**dvancing **N**ovel **D**rugs**)**
Version: 2.0; 09February2015

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Version History:

Version Number/Date	Change
1.0;18January2015	Original
2.0;09February2015	Updates to sample transfer logs

The Quality Control of several parameters occurring during the specimen processing stages of the clinical trial are essential to ensure the consistency and validity of the results obtained.

The points at which factors need to be monitored and recorded will be dealt with by individual procedure. Some of these factors reoccur at several stages throughout the different procedures, such as the need to monitor the temperature of equipment. These will be highlighted in each section, but will have a common Quality Form whenever possible.

The precise location of the work to be undertaken and the staff responsible must be recorded – attachment A

When any Quality Control fails, a Continuous Quality Improvement Form must be completed to document the failure and the corrective action, it also includes a grading system with moderate and severe QC failures being reportable to UCL - attachment N.

Summary of procedures

Sputum Handling

Record the temperature of the package containing the specimens on receipt at the laboratory using an digital minimum/maximum thermometer – attachment B

Sputum Decontamination

Record the pressure of the Containment Level 3 Laboratory, the airflow of the Microbiological Safety Cabinet and the preparation of disinfectants – attachment D.

Record the Lot numbers, expiry date and date of manufacture of the NALC and NaOH – attachment F.

Record the working temperature of the refrigerated centrifuge – attachment F.

Record the temperature of all refrigerators and freezers containing reagents –attachment C.

Record the order samples processed, decontamination times and contamination rates – attachment F

Ziehl-Neelsen (Z-N) Sputum Smear Microscopy

For each new batch of staining reagents perform and record a positive (M. tuberculosis H37Rv) and negative (E. coli) smear – attachment Ei

For each batch of specimens, perform and record a positive (M. tuberculosis H37Rv) and a negative (negative decontamination) smear – attachment H and F respectively.

For every 10 Screening slides compare AFB counts between technicians – Attachment I

HAIN Genotype

Record the internal quality control for the Hain MTBDRplus Test – attachment Li

Record the internal quality control for the Hain MTBDRsl Test – attachment Lii

Record the internal quality control for the Hain MTBC Test – attachment Liii

Liquid Culture by Mycobacteria Growth Indicator Tube (MGIT)

Record the daily maintenance and temperature of the MGIT -attachment J

For each new batch of MGIT bottles and antibiotic supplements record the quality control -attachment Eii

Record the manufacture and Quality Control of the blood agar – attachment Eiii.

Record the temperature of any incubators used – attachment C.

Record the temperature of any refrigerators containing reagents –attachment C.

Record the contamination rates – attachment G

Record details of the contaminated cultures if contamination rates outside 3 – 8% - attachment Gi

Record the Lot number and expiry date of the MGIT calibration tubes – Attachment K

DNA Extraction

Record the estimated DNA concentration for each sample to be shipped to UCL – attachment P

Drug Susceptibility Testing (DST) by Mycobacteria Growth Indicator Tube (MGIT)

Record the pressure of the Containment Level 3 Laboratory, the airflow of the Microbiological Safety Cabinet and the preparation of disinfectants – attachment D.

Record the daily maintenance and temperature of the MGIT -attachment J

Record the MGIT SIRE Drug Susceptibility Testing Internal quality Control (IQC: *M. tuberculosis* H37Rv) – attachment Eiv

Record the MGIT PZA Drug Susceptibility Testing Internal quality Control (IQC: *M. tuberculosis* H37Rv) – attachment Ev

Record the MGIT Moxifloxacin Drug Susceptibility Testing Internal quality Control (IQC: *M. tuberculosis* H37Rv) – attachment Evi

For each new batch of staining reagents perform and record a positive (*M. tuberculosis* H37Rv) and negative (*E. coli*) smear – attachment Ei

Record the manufacture and Quality Control of the blood agar – attachment Eiii.

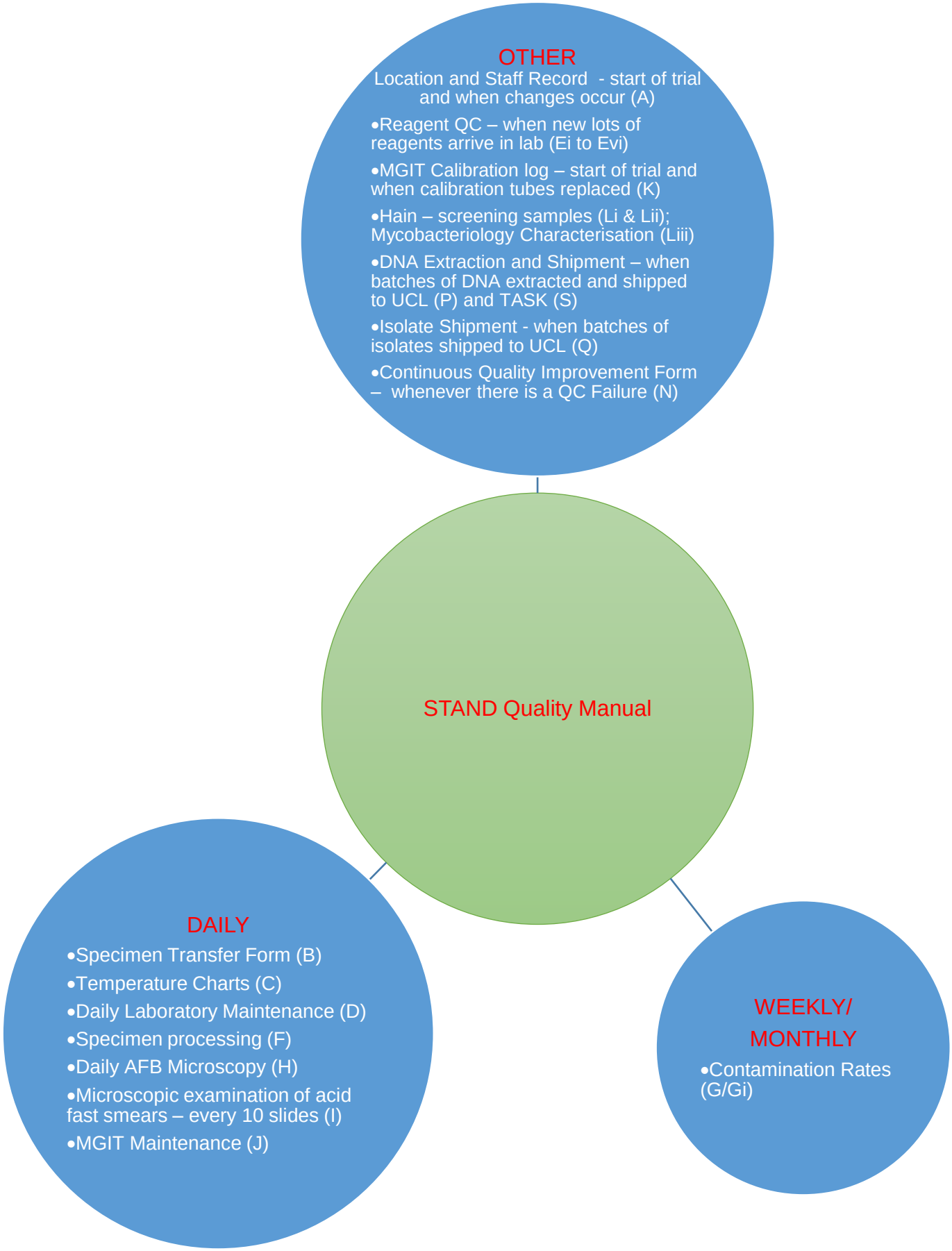
Record the temperature of any incubators used – attachment C.

Record the temperature of any refrigerators and freezers containing reagents –attachment C.

Record the Lot number and expiry date of the MGIT calibration tubes – Attachment K.

MIRU typing of M. tuberculosis

For each new batch of reagents record the quality control – attachment M


OTHER
Location and Staff Record - start of trial and when changes occur (A)
•Reagent QC – when new lots of reagents arrive in lab (Ei to Evi)
•MGIT Calibration log – start of trial and when calibration tubes replaced (K)
•Hain – screening samples (Li & Lii); Mycobacteriology Characterisation (Liii)
•DNA Extraction and Shipment – when batches of DNA extracted and shipped to UCL (P) and TASK (S)
•Isolate Shipment - when batches of isolates shipped to UCL (Q)
•Continuous Quality Improvement Form – whenever there is a QC Failure (N)
STAND Quality Manual
DAILY
•Specimen Transfer Form (B)
•Temperature Charts (C)
•Daily Laboratory Maintenance (D)
•Specimen processing (F)
•Daily AFB Microscopy (H)
•Microscopic examination of acid fast smears – every 10 slides (I)
•MGIT Maintenance (J)
WEEKLY/ MONTHLY
•Contamination Rates (G/Gi)

Attachment A: Location & Staff Record

Location of work		
Full Postal Address	**Room identification (Building & room number)**	**Procedures to be performed (LM number and sections if applicable)**

Laboratory Staff			
Full Name	**Job Title**	**Responsibilities**	**LM sections**

Attachment B: Specimen Transfer Form- **SPUTUM**

This form should accompany each sputum specimen generated from a STAND patient at the clinical site to the laboratory.

Clinical Details

This section should be completed in the clinic

Patient number __ __ __ __ - __ __ __	
Initials	
Date of birth (dd/mmm/yyyy)	
Type of Sputum Sample	☐ Early Morning ☐ Spot
Visit Date (dd/mmm/yyyy)	
Visit in STAND schedule * Week __ __ **OR Month** __ __ Unscheduled treatment phase ☐ Unscheduled post-treatment phase ☐	
Date specimen produced (dd/mmm/yyyy)	
Time specimen produced (hh:mm)	
Physician/nurse attending (print name)	
Physician/nurse attending (signature)	

*screening = SC, baseline = 00

Transport Details

This section should be completed by the driver, courier or person accompanying specimen

Date specimen dispatched from clinic (dd/mmm/yyyy)	
Time specimen dispatched from clinic (hh:mm)	
Temperature of transport container (°C)	
Driver/courier (print name)	
Driver/courier (signature)	

Laboratory Receipt

This section should be completed by the laboratory technician receiving the specimens.

Laboratory Name	
Date sample received (dd/mmm/yyyy)	
Time sample received (hh:mm)	
Temperature of transport container on receipt (°C)	
Sample in good condition (y/n)	
If no *please give details (detail problems, is this sample going to be processed? has another sample been requested?)*	
Sample processed within 30 minutes (yes/no)	
If no, time sample transferred to fridge (hh:mm, and give fridge ID)	
Laboratory technician (print name)	
Laboratory technician (signature)	
Laboratory Accession number	ATTACH LABEL

Attachment C: Equipment Temperature Log Form

EQUIPMENT TYPE and No: **MONTH:** **YEAR:**

LOCATION IN DEPT: **TEMPERATURE RANGE:**

Temperatures should be recorded twice a day at different times each day, when possible.
NOTE: When the temperature is out of range inform the laboratory manager. Refer to site specific SOP for Temperature Monitoring and Evaluation for corrective actions. Record below 'minor' action taken. Record major action on a Continuous Quality Improvement Form (attachment N).
During periods when the lab is not staffed the max and min temperatures over that time period must be recorded in the action box of the last unrecorded date. Draw a line through all other unfilled boxes.

DAY	Temp AM	Time	Signature	Temp PM	Time	Signature	**Action** (for out of range temperatures)
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
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29							
30							
31							

Reviewed by :

Sign: **Date Reviewed:**

Attachment D: Containment Level 3 Laboratory Daily Checklist

'This work area must be clean, uncluttered and well maintained'

- The individual Laboratory Technician MUST date and sign this record upon completion of each housekeeping duty (daily). Records of readings must be noted where applicable.
- The Laboratory Manager MUST date and sign at the end of each week to ensure the duties have been performed.
- All surfaces and the cabinet MUST be disinfected at the end of EACH working day.
- All other areas must be disinfected at least once a week.

Day	Mon	Tue	Wed	Thu	Fri	Sat	Sun
Date							
Pressure with hoods off (<-5Pa)							
Pressure with hoods on (-10 to –60 Pa)							
MSC Reading							
MSC Anemometer Reading (record average of five readings taken at different positions)							
Equipment temperatures acceptable and recorded							
MGIT maintenance performed (checklist completed)							
Fresh disinfectants made (including bottled for MSC)							
Benches and MSC cleaned							
Floor mopped (at least weekly)							
Centrifuge cleaned (at least weekly)							
Laboratory Coats changed (weekly)							
Laboratory Manager – name and date							

If the room pressure or MSC reading is out of range, do not start any work in the laboratory until an appropriately qualified person has fixed the problem and the readings are within range. Record any actions on a continuous quality improvement form (attachment N).

Attachment Ei: Ziehl-Neelsen Stain Reagents

Quality Control Test

Upon receipt of a new shipment or lot number of Carbol Fuschin, Malachite Green/Methylene Blue and/or 3% Acid Alcohol a positive (H37Rv) and negative (E. coli) smear should be made following the laboratory manual guidelines and the results recorded on this worksheet. Record the date the reagent of that lot came into use in the laboratory and the date it finished (this will be used to link reagents used with specimens processed).

Quality Control Results

Both the positive and negative controls must pass for the reagents to be used for staining samples. If the QC fails, repeat the test with new positive and negative controls. If the repeat test fails do not use the reagents and contact the supplier. Any Quality Control Failure and subsequent actions should be recorded on the Continuous Quality Improvement Form (Quality manual attachment N).

Reagent*						
Lot Number						
Expiry Date						
Date QC Test						
Positive Smear Result						
Negative Smear Result						
QC Passed	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Comments						
Staff Signature						
Date						
Date In Use						
Date Finished						

* Carbol Fuschin, Malachite Green/Methylene Blue or 3% Acid Alcohol

Attachment Eii: MGIT TUBES and PANTA/Growth Supplement

Quality Control Test

Upon receipt of a new shipment or lot number of BBL MGIT 7 ml tubes, Growth Supplement and/or PANTA suspensions of *M. tuberculosis* control organism (ATCC 27294 – H37Rv) should be adjusted to 0.5 McFarland, diluted 1:500 in saline and inoculated into MGIT tubes (as described in the operating manual). Record the date the reagent of that lot came into use in the laboratory and the date it finished (this will be used to link reagents used with specimens processed).

Quality Control Results

The BBL MGIT tubes should be detected as positive within 6 – 10 days. If the QC tubes do not give the expected results do not use the remaining tubes of the lot until you have contacted Becton Dickinson Technical services. Any Quality Control Failure and subsequent actions should be recorded on the Continuous Quality Improvement Form (Quality manual attachment N).

Item*					
Lot Number					
Expiry date					
Date of QC Test					
Date Tube Positive					
Time to detection (TTD)					
QC Passed	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Comments					
Staff Initials					
Staff signature					
Date					
Date In Use					
Date Finished					

*MGIT tubes/Growth Supplement/PANTA

Attachment Eiii: Blood Agar Plates

Each time a new lot of commercially prepared plates or batch of blood agar plates are made up in the laboratory the lot numbers, collection dates (for blood if not commercially bought) and expiry dates of each ingredient should be recorded. Record the date the reagent of that lot came into use in the laboratory and the date it finished (this will be used to link reagents used with specimens processed).

Quality Control Test

Inoculate one plate with *Staphylococcus aureus* and leave one plate un-inoculated. After two days check for growth; the plate inoculated with *S. aureus* should show cream coloured colonies, un-inoculated plates should show no growth. If the QC fails, do not use this batch and contact the supplier or prepare a new batch. Any Quality Control Failure and subsequent actions should be recorded on the Continuous Quality Improvement Form (Quality manual attachment N).

Lot Number and Expiry Date (commercially bought plates)						
Batch Number						
Date Batch Prepared						
Blood Agar	**Lot Number**					
	Expiry Date					
Blood	**Lot Number/ Collection Date**					
	Expiry Date					
QC Test – Colonies Visible	***S. aureus* plate**	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
	Un-inoculated plate	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
QC Passed		Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Expiry Date for Batch						
Comments						
Staff Signature						
Date						
Date In Use						
Date Finished						

Attachment Eiv: MGIT SIRE Drug Susceptibility Testing Kit – Only used by UCL Central Laboratory

Quality Control Test

Upon receipt of a new shipment or lot number of MGIT SIRE Kits, positive control testing must be carried out following BD MGIT protocols. Suspensions of *M. tuberculosis* control organism (ATCC 27294 – H37Rv) should be tested as per the normal drug susceptibility testing protocol.

Quality Control Results

The Kits pass if the *M. tuberculosis* H37Rv is fully susceptible to all drugs within 4 – 13 days. If the QC tubes do not give the expected results do not use the SIRE kits of the lot until you have contacted Becton Dickinson Technical services. Any Quality Control Failure and subsequent actions should be recorded on the Continuous Quality Improvement Form (Quality manual attachment N). Record the date the kit of that lot came into use in the laboratory and the date it finished (this will be used to link reagents used with specimens processed).

Lot Number																		
Expiry date (kit)																		
Date of QC Test																		
H37Rv GC TIP																		
H37Rv S/R/C	S	I	R	E	S	I	R	E	S	I	R	E	S	I	R	E	S	I	R	E
QC Passed	Yes ☐ No ☐				Yes ☐ No ☐				Yes ☐ No ☐				Yes ☐ No ☐				Yes ☐ No ☐			
Comments																				
Vials Aliquoted	Yes ☐ No ☐				Yes ☐ No ☐				Yes ☐ No ☐				Yes ☐ No ☐				Yes ☐ No ☐			
Expiry Date of aliquots (6 months if earlier than kit expiry)																				
Staff Initials																				
Staff signature																				
Date																				
Date In Use																				
Date Finished																				

Attachment Ev: MGIT PZA Drug Susceptibility Testing Kit – Only used by UCL Central Laboratory

Quality Control Test

Upon receipt of a new shipment or lot number of MGIT PZA Kits, positive control testing must be carried out following BD MGIT protocols. Suspensions of *M. tuberculosis* control organism (ATCC 27294 – H37Rv) should be tested as per the normal drug susceptibility testing protocol.

Quality Control Results

The Kits pass if the *M. tuberculosis* H37Rv is fully susceptible to PZA within 4 – 20 days. If the QC tubes do not give the expected results do not use the PZA kit of the lot until you have contacted Becton Dickinson Technical services. Any Quality Control Failure and subsequent actions should be recorded on the Continuous Quality Improvement Form (Quality manual attachment N). Record the date the batch of aliquots came into use in the laboratory and the date they finished (this will be used to link reagents used with specimens processed).

Lot Number					
Expiry date (kit)					
Date of QC Test					
H37Rv GC TIP					
H37Rv PZA S/R/C					
QC Passed	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Comments					
Vials Aliquoted	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Expiry Date of aliquots (6 months if earlier than kit expiry)					
Staff Initials					
Staff signature					
Date					
Date in Use					
Date Finished					

Attachment Evi: Quality Control: Moxifloxacin Drug Susceptibility Testing – Only used by UCL Central Laboratory

Quality Control Test

Upon receipt of a new shipment or lot number of Moxifloxacin, positive control testing must be carried out following BD MGIT protocols. Suspensions of *M. tuberculosis* control organism (ATCC 27294 – H37Rv) should be tested as per the normal drug susceptibility testing protocol.

Quality Control Results

The test passes if the *M. tuberculosis* H37Rv is fully susceptible to moxifloxacin within 4 – 13 days. If the QC tubes do not give the expected results do not use the moxifloxacin of the lot until you have contacted the UCL laboratory team. Any Quality Control Failure and subsequent actions should be recorded on the Continuous Quality Improvement Form (Quality manual attachment N). Record the date the batch of aliquots of that lot came into use in the laboratory and the date it finished (this will be used to link reagents used with specimens processed).

Lot Number					
Expiry date (Moxi)					
Date of QC Test					
Amount moxifloxacin weighed (mg) Volume ddH_20 added (ml), detail any further dilutions					
H37Rv GC TIP					
H37Rv MOX S/R/C					
QC Passed	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Comments					
Vials Aliquoted	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Expiry Date of aliquots (6 months if earlier than moxi expiry)					
Staff Initials					
Staff signature					
Date					
Date In Use					
Date Finished					

Attachment F: Processing and Decontaminating Sputum Samples

This quality control form should be completed each day that sputum samples are processed. This form will be used to record the timings of NaOH/NALC decontamination, the order samples are processed including the blank control (placed in the middle of the run). This is a 'decontamination mixture only' control, and should be processed in exactly the same way as the test samples. This negative control will ensure there is no carryover of bacteria between samples (e.g. from contamination of stock solutions), that could result in false positives. MGIT tubes should also be inoculated in the same order (including blank control for MGIT). Record results of negative control for this batch in the table below. If the smears for the negative control fail, new stocks must be prepared and a repeat QC test performed, if it fails again fill out the continuous quality improvement form (send a copy to UCL). *Label all the negative control tubes/slides with date, run/batch number and 'negative control'

Date (dd/mmm/yyyy):	**Run/Batch Number:**
Date NaOH/NALC prepared:	Working Concentration NaOH/NALC:
NaOH Lot No:	NaOH Expiry Date:
NALC Lot No:	NALC Expiry Date:
Sodium Citrate Lot No:	Sodium Citrate Expiry Date:

Staff Name		**Temperature Centrifuge °C:**
Staff Signature		

Order samples processed (max 8 samples only)	**Laboratory Accession Number (for negative control write 'negative')**	**Study (Patient) Number (for negative control write 'negative')**	**Time Decontamination Started (or time on stop clock):** First Sample: Last Sample: **Interval Time:** **Time Decontamination Stopped (or time on stop clock):** First Sample: Last Sample:
1			
2			
3			
4			
5			
6			
7			
8			

Negative Control Results:

	Result +/-	**Staff Name**	**Date**	**Acceptable (y/n)**	**Comments**
ZN Stain					
MGIT Tube no:					
If MGIT positive perform blood agar to distinguish between cross contamination of ***M. tb*** or other contamination:					
Blood Agar				Comments:	
Lab Manager (signature)				**Date**	

Attachment G: Contamination Rates

This QC sheet is used to monitor the contamination rates. The contamination rate should be 3 – 8%. If small numbers of samples, calculate the contamination rate over a longer specified period.
QC Failure: If the contamination rate is below 3% it is possible the samples are being over decontaminated, possibly due to the concentration of NaOH being too high for this population or the time samples are decontaminated is too long. If the samples are consistently contaminated at a rate higher than 8% this could be due to the NaOH solution not being strong enough or the specimens not being decontaminated for long enough.

Period Starting (dd/mmm/yyyy):
Period Finshing (dd/mmm/yyyy):
Weekly ☐ Monthly ☐ Other ☐

	Total Number Completed Tubes (positive and negative) A	**Number (Positive) Tubes Contaminated B**	**Contamination rate % C C = (B/A) x 100**
MGIT			
Contamination Rates between 3 – 8%			Yes ☐ No ☐

IF NO, List ONLY the **contaminated samples** in the table on attachment Gi. The QC Attachment F should be used to check to see if the decontamination times are accurate and the concentration of NaOH/NALC is correct. If this is shown to be accurate, before changing the concentration of the NaOH/NALC a quality control improvement form should be completed, requesting such a change and sent with this form to the UCL Laboratory Team for review and action.

Attachment Gi Completed	Yes ☐ No ☐

Comments:

Staff Name	
Staff Signature	

Attachment Gi: Contaminated Samples
Only complete this form if the contamination rate is outside 3 – 8% (form G).

Period Starting (dd/mmm/yyyy):
Period Finishing (dd/mmm/yyyy):
MGIT Contamination Rate (%):

Laboratory Accession Number	**Study (Patient) Number**	**Sputum processed**		Order Number in Decon Process	**Decon. Time (min)**	**NaOH/NALC**		**Neg control contaminated y/n**	**Staff Name (decontamination process)**
		Date	Batch No.			Conc.	Prep. date		
Staff Name: Staff Signature:									

Attachment H: Daily AFB Microscopy

Quality Control Test

Every time smears are stained a positive control slide (*M.tb* H37Rv) MUST be included and the results reported in the table below.

If MORE THAN ONE sputum is being processed at a time, a negative control sample must also be prepared and stained, the results should be recorded on attachment F.

Quality Control Results

The positive control slide must pass for the microscopy results to be reported. If the positive QC fails new smears must be prepared and re-stained, check that the attachment Ei has been completed and passed for these batches of reagents. Any Quality Control Failure and subsequent actions should be recorded on the Continuous Quality Improvement Form (Quality manual attachment N).

Date	Batch Number	Positive Control Result (Ziehl-Neelsen)	Staff Name and Signature

Attachment I: Microscopic Examination of Acid-Fast Smears

For every tenth slide examined there will be a two-person comparison recorded in the table below. When the second person examines the slide they should not know the initial result

Initials Lab Staff 1	Date	Slide Laboratory Accession No.	Screening No.	Av. No. AFBs (over 100 fields)	WHO/IUATLD Reporting*	Initials Lab Staff 2	Date	Slide Laboratory Accession No.	Screening No.	Av. No. AFBs (over 100 fields)	WHO/IUATLD Reporting*	Comparison acceptable y/n

* not seen / scanty / 1+ / 2+ / 3+

The results for the WHO/IUATLD reporting column should be the same for both counts. If results do not compare inform the Laboratory Manager. The counts should be repeated and confirmed by a third person and staff retrained. Please describe action taken in Continuous Quality Improvement Form, attachment N.

Attachment J: MGIT 960 Daily Maintenance Log

(Month/Year) __ __ __ **/** __ __ __ __

This Log should be filled out daily (a line should be drawn through weekends and public holidays if not done). If any of the sections fail inform the Laboratory Manager. Refer to the MGIT Standard Operating Procedure and/or Operating Manual for troubleshooting. If this fails contact the local Becton Dickinson representative. Any Quality Control Failure and subsequent actions should be recorded on the Continuous Quality Improvement Form (Quality manual attachment N).

Date	Check printer paper	Check Temperature Probes 37 °C + 1 / - 2 °C			Check Drawer Indicators			Check Station Indicators			Initials	Monthly – clean/replace air filters
								A	B	C		
		A	B	C	A	B	C	R/G	R/G	R/G		
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												Initials
11												Date
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Attachment K: MGIT Calibration Tube Log

This log should be used to track the expiry date and replacement dates for the MGIT calibration tubes. Calibration tubes should be replaced before they are due to expire. Contact your local Becton Dickinson representative for ordering information.

Calibrator Station	Current Lot number/Expire date	Date replaced	New Lot number/Expire date
A/A00			
A/B00			
A/C00			
A/D00			
A/E00			
A/F00			
A/G00			
A/H00			
A/J00			
A/K00			
A/L00			
A/M00			
A/N00			
A/P00			
A/R00			
A/S00			
B/A00			
B/B00			
B/C00			
B/D00			
B/E00			
B/F00			
B/G00			
B/H00			
B/J00			
B/K00			
B/L00			
B/M00			
B/N00			
B/P00			
B/R00			
B/S00			
C/A00			
C/B00			

C/C00			
C/D00			
C/E00			
C/F00			
C/G00			
C/H00			
C/J00			
C/K00			
C/L00			
C/M00			
C/N00			
C/P00			
C/R00			
C/S00			
Delegated Laboratory Staff (printed name)			
Delegated Laboratory Staff (signature)			

Attachment Li: GenoType® MTBDR*plus*

Procedure	Performed By (Name)	Date of Test	Product detail	Product Lot Number	Product Expiry Date	Equipment	Recorded Temp °C
DNA Extraction			N/A	N/A	N/A	Heating Block/Water bath	
Amplification			Primer Nucleotide Mix (PNM)			N/A	N/A
			DNA Taq Polymerase			N/A	N/A
Hybridisation			GenoType® MTBDRplus Kit			Waterbath/Twincubator	
						Substrate Incubation	Time (min)

Evaluation of Results performed by _____Date _____ Evaluation Sheet No:

Strip No	Screening Number	Laboratory Accession Number	Control Bars Visible (y/n)					Result accepted yes/no	Comments
			CC	AC	LC rpoB	LC katG	LC inhA		
	POSITIVE CONTROL (H37Rv)								
	NEGATIVE CONTROL (ddH_2O)								

CC – conjugate control, AC – amplification control, LC – locus control, S – sensitive, R – resistant, y – yes, n – no

If there is a QC failure refer to the STAND Laboratory Manual or MTBDRp*lus* User guide for troubleshooting options, record all actions on the Continuous Quality Improvement Form (Quality manual attachment N). If this does not resolve the issue send this form and the attachment N to UCL stating the QC failure.

Attachment Lii: GenoType® MTBDR*sl*

Procedure	Performed By (Name)	Date of Test	Product detail	Product Lot Number	Product Expiry Date	Equipment	Recorded Temp °C
DNA Extraction			N/A	N/A	N/A	Heating Block/Water bath	
Amplification			Primer Nucleotide Mix (PNM)			N/A	N/A
			DNA Taq Polymerase			N/A	N/A
Hybridisation			GenoType® MTBDRsl Kit			Waterbath/Twincubator	
						Substrate Incubation	Time (min)

Evaluation of Results performed by _____Date _____ Evaluation Sheet No:

Strip No	Screening Number	Laboratory Accession Number	Control Bars Visible (y/n)					Result accepted yes/no	Comments
			CC	AC	LC gyrA	LC rrs	LC emb B		
	POSITIVE CONTROL (H37Rv)								
	NEGATIVE CONTROL (ddH_2O)								

CC – conjugate control, AC – amplification control, LC – locus control, S – sensitive, R – resistant, y – yes, n – no

If there is a QC failure refer to the STAND Laboratory Manual or MTBDR*sl* User guide for troubleshooting options, record all actions on the Continuous Quality Improvement Form (Quality manual attachment N). If this does not resolve the issue send this form and the attachment N to UCL stating the QC failure.

Attachment Liii: GenoType® MTBC – Only used by UCL Central Laboratory

Procedure	Performed By (Name)	Date of Test	Product detail	Product Lot Number	Product Expiry Date	Equipment	Recorded Temp °C
DNA Extraction			N/A	N/A	N/A	Heating Block/Water bath	
Amplification			Primer Nucleotide Mix (PNM)			N/A	N/A
			DNA Taq Polymerase			N/A	N/A
Hybridisation			GenoType® MTBC Kit			Waterbath/Twincubator	
						Substrate Incubation	Time (min)

Evaluation of Results performed by _____Date _____ Evaluation Sheet No:

Strip No	Patient Number	Laboratory Accession Number	Control Bars Visible (y/n)			Result accepted yes/no	Comments
			CC	UC	MTBC		
	POSITIVE CONTROL (H37Rv)						
	NEGATIVE CONTROL (ddH_2O)						

CC – conjugate control, UC – universal control, LC – locus control, MTBC – mycobacterium tuberculosis complex S – sensitive, R – resistant, y – yes, n – no

If there is a QC failure refer to the STAND Laboratory Manual or MTBC User guide for troubleshooting options, record all actions on the Continuous Quality Improvement Form (Quality manual attachment N). If this does not resolve the issue send this form and the attachment N to UCL stating the QC failure.

Attachment M: MIRU Typing – Only used by UCL Central Laboratory

Quality Control Test

Upon receipt of a new shipment or lot number of Qiagen HotStarTaq, dNTPs, Primer mixes 1-8 or MIRU ladder, a PCR amplification of a positive control (M.tb H37Rv DNA) and negative control (UV-treated water) should be analysed following the STAND MIRU SOP (SOP 13) and the results recorded on this worksheet. Record the date the reagent of that lot came into use in the laboratory and the date it finished.

Quality Control Results

The positive control must match the H37Rv genotype in SOP 13 and the negative control should have no detectable DNA products for the reagents to be used for the analysis of trial samples. QC data should be filed with the Quality Control Forms. If the QC fails, repeat the test with new positive control. If the repeat test fails do not use the reagents and contact the supplier. Any Quality Control Failure and subsequent actions should be recorded on the Continuous Quality Improvement Form (Quality manual attachment N).

Reagent						
Lot Number						
Expiry Date						
Date QC Test						
QC Passed (Positive and Negative Controls)	**Yes □ No □**	**Yes □ No □**	**Yes □ No □**	**Yes□ No □**	**Yes □ No □**	**Yes □ No**
Comments						
Staff Signature						
Date						
Date In Use						
Date Finished						

Attachment N: Continuous Quality Improvement Form

This form should be completed every time there is a QC failure.

Continuous Quality Improvement Form N°:

Categorise QC Failure:

☐ **Severe**

Likely to result in exclusion of data, unable to resolve in-house, likely to delay processing of samples, requires amendment to laboratory manual and/or STAND protocol, repeat QC failure.

Contact UCL Laboratory Team immediately before taking any action, complete section 1 and send (scan) this document and QC form showing failure

☐ **Moderate**

Does not affect data or delay processing samples, can repeat analysis if necessary, able to resolve in-house by laboratory management and/or Quality Assurance officer, same QC failure may have occurred on more than one occasion, does not require amendment to laboratory manual and/or protocol.

Resolve problem in-house, complete this form but contact and send to UCL Laboratory team to make aware

☐ **Mild**

Does not affect data or processing samples, easily resolved in-house by laboratory staff, one-off QC failure. *Resolve in-house, complete and file this form, no need to contact UCL*

1. Description of QC Failure

QC Form:_____ Date QC Failure:_____

Print Name & Sign: Date:

2. Detail In-house Action to Fix Immediate Problem

Print Name & Sign: Date:

3. Root Cause(s) of the Problem

Print Name & Sign: Date:

4. Action Required to Eliminate the Root Causes (and Implementation Timeframe)

Print Name & Sign: Date:

5. Action Taken to Verify Effectiveness of Action (and changes to documentation if necessary)

Print Name & Sign: Date:

Attachment P: DNA extraction and shipment to UCL

This form should be completed each time DNA isolates are to be shipped to UCL. Estimated DNA concentration should be performed after DNA extraction and the values used to complete the table below. Total DNA exceeding 1 µg total per sample is required. A copy of this form should be sent with the DNA samples. The samples should be sent on a 6 weekly basis but should not be sent if less than 20 samples per shipment. The samples should be shipped at below room temperature (wet ice or colder).

Site/Laboratory Name:
Shipment Date:
Total Number Tubes:

Patient Number	Patient Initials	Visit Schedule	Sample Collection Date	Laboratory Accession Number	A Estimated DNA Concentration (ng/µL)	B Estimated Volume (µL)	C Estimated Total DNA (µg) C = (A x B)/1000

Staff Name;	**Staff Signature:**

Attachment Q: Isolate Shipment to UCL

This form should be completed each time isolates are to be shipped to UCL. A copy of this form should be sent with the LJ cultures. The samples should be sent on a 6 weekly basis. The samples should be shipped at room temperature and packaged according to Category A - Infectious

Site/Laboratory Name:
Shipment Date:
Total Number Tubes:

Patient Number	Laboratory Accession Number	Patient Initials	Specimen Type	Visit Schedule	Sample Collection Date and Time

Staff Name;	**Staff Signature:**

Attachment S: DNA Shipment to TASK for *pncA* Sequencing

This section should be completed by the local mycobacteriology laboratory. Once completed, this log should be scanned and emailed to the TASK laboratory. The hardcopy should be kept on-site, and an additional copy must be given to the courier.

Name of Local Mycobacteriology Laboratory		Log Sheet Number	
Date			

TUBE #	LOCAL MYCOBACTERIOLOGY LABORATORY ACCESSION NUMBER	PATIENT NUMBER	PATIENT INITIALS	DATE DNA EXTRACTED
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				

Total amount of DNA samples to be shipped	
Log Sheet Number (as per page 1) If there are more than 12 samples in total, the front page must be printed and the log sheet number should be reported as "1of2" and "2of 2", if two front pages are required. If there are less than12 samples in total, the log sheet number should be reported as "1 of 1".	
Date DNA Sample Transport Log was scanned and emailed to TASK	(dd/mmm/yy) ☐☐ ☐☐☐ ☐☐
Time DNA Sample Transport Log was scanned and emailed to TASK	(hh:mm) ☐☐ ☐☐
Name of Technologist who scanned and emailed the DNA Sample Transport Log to the TASK (print name)	
Signature of Technologist who scanned and emailed the DNA Sample Transport Log to the TASK	
Date that both the DNA and the DNA Sample Transport Log was handed over to courier	(dd/mmm/yy) ☐☐ ☐☐☐ ☐☐
Time that both the DNA and the DNA Sample Transport Log was handed over to courier	(hh:mm) ☐☐ ☐☐
Name of Technologist who handed over the packaged DNA and DNA Sample Transport Log to the courier (print name)	
Signature of Technologist who handed over the packaged DNA and DNA Sample Transport Log to the courier	

Courier Services

This section must be completed by the Courier **EXPORTING** the material

Date that both the DNA and the DNA Sample Transport Log was received by the courier	(dd/mmm/yy) ☐☐ ☐☐☐ ☐☐
Time that both the DNA and the DNA Sample Transport Log was handed over to courier	(hh:mm) ☐☐ ☐☐
Name of Courier who received the packaged DNA and DNA Sample Transport Log (print name)	
Signature of Courier who received the packaged DNA and DNA Sample Transport Log	

This section must be completed by the Courier **IMPORTING** the material.

Date that Courier delivered the packaged DNA and the DNA Sample Transport Log at the TASK	(dd/mmm/yy) ☐☐ ☐☐☐ ☐☐
Time that Courier delivered the packaged DNA and the DNA Sample Transport Log at the TASK	(hh:mm) ☐☐ ☐☐
Name of Courier who delivered the packaged DNA and DNA Sample Transport Log (print name)	
Signature of Courier who delivered the packaged DNA and DNA Sample Transport Log	

TASK Laboratory Receipt

This section should be completed by the TASK laboratory reception officer, or designated other, where the packaged DNA and DNA Sample Transport Log are received.
Once a TASK accession number has been generated, a worksheet must be drawn up which will contain all the samples received from all referral laboratories on a specific day. Once the worksheet has been created, the DNA specimens must be placed in order as they appear on the worksheet that was generated by the reception officer on that specific day. The worksheet and DNA is to be handed over to the molecular division to check that the DNA was placed in the correct order by the reception officer, after TASK laboratory accession numbers has been generated.

Date that Courier delivered the packaged DNA and the DNA Sample Transport Log hardcopy	(dd/mmm/yy) ☐☐ ☐☐☐ ☐☐
Time that Courier delivered the packaged DNA and the DNA Sample Transport Log hardcopy	(hh:mm) ☐☐ ☐☐
Name of reception officer who received the packaged DNA and DNA Sample Transport Log (print name)	
Signature of reception officer who received the packaged DNA and DNA Sample Transport Log	
Date that electronic copy (emailed) DNA Sample Transport Log was received at reception	(dd/mmm/yy) ☐☐ ☐☐☐ ☐☐
Time that electronic copy (emailed) DNA Sample Transport Log was received at reception	(hh:mm) ☐☐ ☐☐
Name of reception officer who received email notification of the anticipated DNA Samples (print name)	
Signature of reception officer who received email notification of the anticipated DNA Samples	
Courier Turn-around time (TAT) - Time from email notification by referral laboratory to receipt of DNA samples at TASK	☐☐ ys ☐☐ ☐☐
Test samples from this shipment added to other test sample shipments arriving on the same day and arranged in order to match the *pncA* amplification worksheet that was created from all the DNA samples received on this day	☐ Yes ☐ No
pncA Amplification worksheet number (The daily worksheet to which the samples of this shipment has been added to)	
Date that DNA samples and *pncA* amplification worksheet that was created were given to the molecular division by the reception officer	(dd/mmm/yy) ☐☐ ☐☐☐ ☐☐
Time that DNA samples and *pncA* amplification worksheet that was created were given to the molecular division by the reception officer	(hh:mm) ☐☐ ☐☐
Name of reception officer who gave the DNA samples and the *pncA* amplification worksheet to the molecular division (print name)	
Signature of reception officer who gave the DNA samples and the *pncA* amplification worksheet to the molecular division	

pncA Sequencing

This section should be completed by the molecular division supervisor, or designated other, of the TASK laboratory, where the packaged DNA and DNA Sample Transport Log are received.

Date that DNA samples were given to the molecular division for *pncA* amplification and subsequent HRM analysis	(dd/mmm/yy) ☐☐ ☐☐☐ ☐☐
Time that DNA samples were given to the molecular division for *pncA* amplification and subsequent HRM analysis	(hh:mm) ☐☐☐☐
Name of technologist who received the DNA samples for *pncA* amplification and subsequent HRM analysis (print name)	
Signature of technologist who received the DNA samples for *pncA* amplification and subsequent HRM analysis	
Date that *pncA* amplification and subsequent HRM analysis was done	(dd/mmm/yy) ☐☐ ☐☐☐ ☐☐
Time that *pncA* amplification and subsequent HRM analysis was done	(hh:mm) ☐☐☐☐
Name of technologist who performed the *pncA* amplification and subsequent HRM analysis (print name)	
Signature of technologist who performed the *pncA* amplification and subsequent HRM analysis	

All the samples that had a positive signal for the successful amplification of the *pncA* gene in *M. tuberculosis* are to be sent for *pncA* sequencing using the TASK local form **TMTF NC006-003 "Sample Transport Log for *pncA* Sequencing**".

Those which gave a negative signal for the *pncA* gene will be subjected to a repeat pncA amplification step and the HRM will be repeated.