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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Van Aartsen D, Justin M, Mduma E, et al.Enteropathogen spectrum and effect on antimycobacterial pharmacokinetics among children with tuberculosis in rural Tanzania: a prospective cohort study. *Lancet Microbe* 2022; published online April 7. https://doi.org/10.1016/S2666-5247(21)00308-6.

Supplementary Material

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Supplementary Tables

Supplemental Table 1. Weight based dosing of anti-TB medications using paediatric non-dispersible formulations (2-20kg)[1,2]

Weight (kg)	Intensive phase (2 months)		Continuation phase (4 months)
	RHZ (paediatric) 60/30/150mg	Ethambutol (100mg)	RH (paediatric) 60/30mg
2-2.9	½ tablet	½ tablet	½ tablet
3-3.9	1 tablet	½ tablet	1 tablet
4-5.9	1 tablet	1 tablet	1 tablet
6-7.9	1.5 tablets	1.5 tablets	1.5 tablets
8-10.9	2 tablets	2 tablets	2 tablets
11-13.9	3 tablets	3 tablets	3 tablets
14-19.9	4 tablets	4 tablets	4 tablets

Supplemental table 2. Weight based dosing of anti-TB medications using adult FDC formulations (≥5 kg)[2]

Weight (kg)	Intensive phase (2 months)	Continuation phase (4 months)
	RHZE (adult) 150/75/400/275 mg	RH (adult) 150/75mg
5-9.9	½ tablet	Use paediatric formulation; if not available, ½ tablet adult
10-14.9	1 tablet	Use paediatric formulation; if not available, 1 tablet adult
15-19.9	1.5 tablets	Use paediatric formulation; if not available, 1.5 tablets adult
20-24.9	2 tablets	2 tablets
25-29.9	2.5 tablets	2.5 tablets
30-40	3 tablets	3 tablets
>40	4 tablets	4 tablets

Practical Guidance for administering non-dispersible formulations to children[2]:

- Crush tablets to ensure that the entire pill portion is retained (e.g., crush between two spoons and insert both spoons into a liquid or soft food to collect the powder from both).
- Crush hard tablets by placing the tablet between a clean, folded sheet of paper and rolling a hard round object over it, making certain not to tear the paper. Funnel the powder into a liquid or soft food substance.
- Mix the crushed tablet with clean (ideally, boiled) water (that has cooled to room temperature) or bottled water.
- Crushed pills can have a bitter taste, and the child may spit up or vomit the dose.
    - If the child spits up or vomits their dose less than 30 minutes after receiving it, repeat the dose immediately, mixing it with a different liquid or soft food.
    - If the child vomits more than 30 minutes after receiving the dose, it should not be re-administered. In both instances, the next dose should be given as scheduled.

Supplemental Table 3. Weight-based dosing of dispersible formulation of anti-TB drugs for children (0-24.9 kg body weight)[3]

Weight (kg)	Intensive phase (2 months)		Continuation phase (4 months)
	RHZ (paediatric) 75/50/150mg	Ethambutol (100mg)	RH (paediatric) 75/50 mg
<4kg **	For infants below 4 kg, consult a pediatric specialist, DTLC, and RTLC for treatment advice.		
2-2.9	½ tablet	½ tablet	½ tablet
3-3.9	1 tablet	½ tablet	1 tablet
4-7.9	1 tablet	1 tablet	1 tablet
8-11.9	2 tablets	2 tablets	2 tablets
12-15.9	3 tablets	3 tablets	3 tablets
16-24.9	4 tablets	4 tablets	4 tablets
≥25	Use adult FDCs		

Practical guidance for administering medicines to children[3]:

- Pediatric FDCs (RHZ and RH) are dispersible in liquid and fruit-flavored as to be more palatable to children to improve ease of administration for parents and children. In addition to dissolving in liquid, the

pediatric FDC tablets can also be swallowed normally. For paediatric RHZ and RH, advise parents/caregivers to:

- Dissolve the tablets in clean, safe water (approximately 50mL); it will then be ready to drink after 10 seconds
- Once dissolved, it should be drunk within 10 minutes
- Entire volume of liquid must be finished by the child to ensure entire dose is given
- If the child spits up or vomits their dose less than 30 minutes after receiving it, re-administer another dose immediately by mixing it with a different liquid.
- If the child vomits more than 30 minutes after receiving the dose, it has already been absorbed and should not be re-administered

For paediatric ethambutol (film-coated), advise parents/caregivers to[3]:

- Attempt to have child swallow ethambutol tabs; if child is unable to swallow, ethambutol can be crushed and mixed with liquid (but crushing may reduce its effectiveness and potency)
- If the child spits up or vomits their dose less than 30 minutes after receiving it, re-administer another dose immediately.
- If the child vomits more than 30 minutes after receiving the dose, it has already been absorbed and should not be re-administered

All TB medications are procured through the Global Drug Facility by the Tanzanian Ministry of Health. The manufacturer for all formulations was Lupin Limited, Mumbai, India.

Supplemental Table 4. Primer and probe sequences for TaqMan real time PCR assays used on TaqMan Array Card.

	Pathogen	Gene	Strand	Sequence used on TAC
Virus	Adenovirus 40/41	Fiber gene	forward	AACTTTCTCTCTTAATAGACGCC
			reverse	AGGGGGCTAGAAAACAAAA
			probe	CTGACACGGGCACTCT
	Astrovirus	Capsid	forward	CAGTTGCTTGCTGCGTTCA
			reverse	CTTGCTAGCCATCACACTTCT
			probe	CACAGAAGAGCAACTCCATCGC
	Norovirus GI	ORF1-2	forward	CGYTGGATGCGNTTYCATGA
			reverse	CTTAGACGCCATCATCATTYAC
			probe	TGGACAGGAGATCGC
	Norovirus GII	ORF1-2	forward	CARGARBCNATGTTYAGRTGGATGAG
			reverse	TCGACGCCATCTTCATTCACA
			probe	TGGGAGGGCGATCGCAATCT
	Rotavirus	NSP3	forward	ACCATCTWCACRTRACCCTCTATGAG
			reverse	GGTCACATAACGCCCCTATAGC
			probe	AGTTAAAAGCTAACACTGTCAAA
	Sapovirus	RdRp	forward	GAYCASGCTCTCGCYACCTAC
			forward	TTGGCCCTCGCCACCTAC
			reverse	CCCTCCATYTCAAACACTA
			probe	CCRCCTATRAACCA
Bacteria	EAEC	aaiC	forward	ATTGTCCTCAGGCATTTCAC
			reverse	ACGACACCCCTGATAAACAA
			probe	TAGTGCATACTCATCATTTAAG
		aatA	forward	CTGGCGAAAGACTGTATCAT
			reverse	TTTTGCTTCATAAGCCGATAGA
			probe	TGGTTCTCATCTATTACAGACAGC
	EPEC	eae	forward	CATTGATCAGGATTTTTCTGGTGATA
			reverse	CTCATGCGGAAATAGCCGTTA
			probe	ATACTGGCGAGACTATTTCAA
		bfpA	forward	TGGTGCTTGCGCTTGCT
			reverse	CGTTGCGCTCATTACTTCTG
			probe	CAGTCTGCGTCTGATTCCAA
	ETEC	LT	forward	TTCCCACCGGATCACCAA
			reverse	CAACCTTGTGGTGCATGATGA
			probe	CTTGGAGAGAAGAACCCT
		STh	forward	GCTAAACCAGYAGRGTCTTCAAAA
			forward	CCCGGTACARGCAGGATTACAACA
			reverse	TGGTCCTGAAAGCATGAA

		STp	reverse	TGAATCACTTGACTCTTCAAAA
			probe	GGCAGGATTACAACAAAGTT
			probe	TGAACAACACATTTTACTGCT
	STEC	*stx1*	forward	ACTTCTCGACTGCAAAGACGTATG
			reverse	ACAAATTATCCCCTGWGCCACTATC
			probe	CTCTGCAATAGGTACTCCA
		stx2	forward	CCACATCGGTGTCTGTTATTAACC
			reverse	GGTCAAAACGCGCCTGATAG
			probe	TTGCTGTGGATATACGAGG
	Aeromonas	Aerolysin	forward	TYCGYTACCAGTGGGACAAG
			reverse	CCRGCAAACTGGCTCTCG
			probe	CAGTTCCAGTCCCACCACTT
	C. jejuni/C. coli	cadF	forward	CTGCTAAACCATAGAAATAAAATTTCTCAC
			reverse	CTTTGAAGGTAATTTAGATATGGATAATCG
			probe	CATTTTGACGATTTTTGGCTTGA
	Campylobacter spp.	Cpn60	forward	AAAGTIGGMAAAGATGGTGTTAT
			forward	AAAGTIGGWAAAGACGGYGTTAT
			reverse	TCAAATTGCATACCYTCAAC
			probe	TTTGCCTCTTCMACAGT
			probe	TTTGCTTCTTCWACAGT
			probe	TAAGCTCCAACTTCATCCG
	Clostridium difficile	tcdB	forward	GGTATTACCTAATGCTCCAAATAG
			reverse	TTTGTGCCATCATTTTCTAAGC
			probe	CCTGGTGTCCATCCTGTTTC
		tcdA	forward	TTCAAGCAGAAATAGAGCACTC
			reverse	TATCAGCCCATTGTTTTATGTATTC
			probe	CACTGACTTCTCCACCTATCCA
	Helicobacter pylori	ureC	forward	GACACCAGAAAAAGCGGCTA
			reverse	AGCGCATGTCTTCGGTTAAA
			probe	TCACTAAAGCGTTTTCTACC
	Mycobacterium tuberculosis	IS6110	forward	GGGTAGCAGACCTCACCTATG
			reverse	AGCGTAGGCGTCGGTGA
			probe	TCGCCTACGTGGCCTTT
	Plesiomonas shigelloides	*gyrB*	forward	CCGCCGTGAAGGCAAAG
			reverse	GCTACCGGCTCACCCAGAT
			probe	CACACCCAAGAATAC
	Salmonella enterica	*ttr*	forward	CTCACCAGGAGATTACAACATGG
			reverse	AGCTCAGACCAAAAGTGACCATC
			probe	CACCGACGGCGAGACCGACTTT
	Shigella/EIEC	*ipaH*	forward	CCTTTTCCGCGTTCCTTGA
			reverse	CGGAATCCGGAGGTATTGC
			probe	CGCCTTTCCGATACCGTCTCTGCA
Fungi	*Encephalitozoon intestinalis*	SSU rRNA	forward	TGTGTAGGCGTGAGAGTGTATCTG
			reverse	CATCCAACCATCACGTACCAATC
			probe	CACTGCACCCACATCCCTCACCCTT
	Enterocytozoon bieneusi	*ITS*	forward	CACCAGGTTGATTCTGCCTGAC
			reverse	CTAGTTAGGCCATTACCCTAACTACCA
			probe	CTATCACTGAGCCGTCC
Protozoa	*Cryptosporidium* spp.	18S rRNA	forward	GGGTTGTATTTATTAGATAAAGAACCA
			reverse	AGGCCAATACCCTACCGTCT
			probe	TGACATATCATTCAAGTTTCTGAC
	Entamoeba histolytica	18S rRNA	forward	ATTGTCGTGGCATCCTAACTCA
			reverse	GCGGACGGCTCATTATAACA
			probe	TCATTGAATGAATTGGCCATTT
	Giardia spp.	18S rRNA	forward	GACGGCTCAGGACAACGGTT
			reverse	TTGCCAGCGGTGTCCG
			probe	CCCGCGGCGGTCCCTGCTAG
	Cyclospora cayetanensis[¶]	18S rRNA (2)	forward	AAAAGCTCGTAGTTGGATTTCTG
			reverse	AACACCAACGCACGCAGC
			probe	AAGGCCGGATGACCACGA
	Cystoisospora belli	18S rRNA	forward	ATATTCCCTGCAGCATGTCTGTTT
			reverse	CCACACGCGTATTCCAGAGA
			probe	CAAGTTCTGCTCACGCGCTTCTGG
Helminth	*Ancylostoma duodenale*	*ITS2*	forward	GAATGACAGCAAACTCGTTGTTG
			reverse	ATACTAGCCACTGCCGAAACGT
			probe	ATCGTTTACCGACTTTAG
	Necator americanus	*ITS2*	forward	CTGTTTGTCGAACGGTACTTGC
			reverse	ATAACAGCGTGCACATGTTGC
			probe	CTGTACTACGCATTGTATAC
	Ascaris lumbricoides	*ITS1*	forward	GCCACATAGTAAATTGCACACAAAT

			reverse	GCCTTTCTAACAAGCCCAACAT
			probe	TTGGCGGACAATTGCATGCGAT
	Strongyloides stercoralis	Dispersed	forward	TCCAGAAAAGTCTTCACTCTCCAG
		repetitive	reverse	TGCGTTAGAATTTAGATATTATTGTTGCT
		sequence	probe	TCAGCTCCAGTTGAACAACAGCCTCCAA
	Trichuris trichiurs	18S rRNA	forward	TTGAAACGACTTGCTCATCAACTT
			reverse	CTGATTCTCCGTTAACCGTTGTC
			probe	CGATGGTACGCTACGTGCTTACCATGG
Control	MS2	*MS2g1*	forward	TGGCACTACCCCTCTCCGTATTCAC
			reverse	GTACGGGCGACCCCACGATGAC
			probe	CACATCGATAGATCAAGGTGCCTACAAGC
	PhHV	*gB*	forward	GGGCGAATCACAGATTGAATC
			reverse	GCGGTTCCAAACGTACCAA
			probe	TATGTGTCCGCCACCATCT

Primer and probe sequences are as previously described[4]. Full methods and protocol are as previously published.[4]

Supplemental Table 5. Effect of enteropathogen burden on peak serum drug concentration (C_{max}) and area under the concentration curve (AUC_{0-24}) in bivariable analysis.

Pharmacokinetic Outcome	**Model**	**Estimated percent change**	**95% CI Lower Bound**	**95% CI Upper Bound**	***p* value**
Rifampicin C_{max}	All	-20.0	-38.5	4.0	0.0937
Isoniazid C_{max}	All	-16.6	-32.5	3.0	0.0899
Pyrazinamide C_{max}	All	-15.8	-36.0	10.9	0.214
Ethambutol C_{max}	All	-10.5	-25.2	7.1	0.22
Rifampicin C_{max}	Bacterial	-25.6	-48.6	7.5	0.113
Isoniazid C_{max}	Bacterial	-5.4	-30.3	28.4	0.714
Pyrazinamide C_{max}	Bacterial	-15.1	-43.0	26.5	0.41
Ethambutol C_{max}	Bacterial	-17.8	-36.0	5.6	0.121
Rifampicin C_{max}	Viral	-27.9	-62.8	39.6	0.323
Isoniazid C_{max}	Viral	-40.1	-64.2	0.2	0.0507
Pyrazinamide C_{max}	Viral	29.5	-34.3	155.3	0.445
Ethambutol C_{max}	Viral	-21.6	-49.9	22.5	0.276
Rifampicin C_{max}	Parasitic	20.2	-32.5	114.1	0.523
Isoniazid C_{max}	Parasitic	2.5	-35.7	63.4	0.916
Pyrazinamide C_{max}	Parasitic	-29.5	-61.9	30.7	0.258
Ethambutol C_{max}	Parasitic	5.6	-30.3	60.1	0.791
Rifampicin AUC_{0-24}	All	-17.0	-37.3	10.0	0.188
Isoniazid AUC_{0-24}	All	-1.7	-24.5	28.0	-0.894
Pyrazinamide AUC_{0-24}	All	-14.1	-30.3	5.8	0.147
Ethambutol AUC_{0-24}	All	-22.4	-40.0	0.2	-0.0514
Rifampicin AUC_{0-24}	Bacterial	-15.8	-43.6	25.5	0.387
Isoniazid AUC_{0-24}	Bacterial	29.0	-10.5	85.9	0.166
Pyrazinamide AUC_{0-24}	Bacterial	-21.3	-41.7	6.2	0.113
Ethambutol AUC_{0-24}	Bacterial	-13.2	-36.7	19.0	0.363
Rifampicin AUC_{0-24}	Viral	-26.6	-62.7	44.1	0.358
Pyrazinamide AUC_{0-24}	Viral	3.6	-37.0	70.5	0.885
Ethambutol AUC_{0-24}	Viral	-53.2	-70.7	-25.2	0.0028

Rifampicin AUC_{0-24}	Parasitic	1.1	-45.9	89.0	0.971
Isoniazid AUC_{0-24}	Parasitic	-14.5	-50.4	47.6	0.565
Pyrazinamide AUC_{0-24}	Parasitic	-6.9	-41.0	46.8	0.751
Ethambutol AUC_{0-24}	Parasitic	10.3	-32.2	79.4	0.682

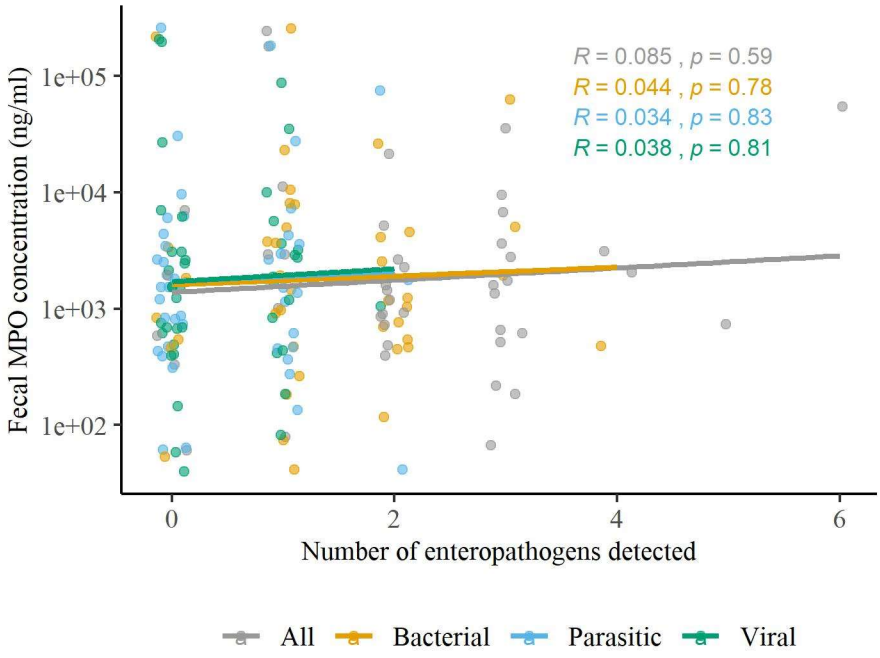
Log-C_{max} and log-AUC_{0-24} were modeled as functions of enteropathogen burden. Effect size reported is the relative change in C_{max} or AUC_{0-24} associated with detection of an additional pathogen in bivariable analyses.

References:

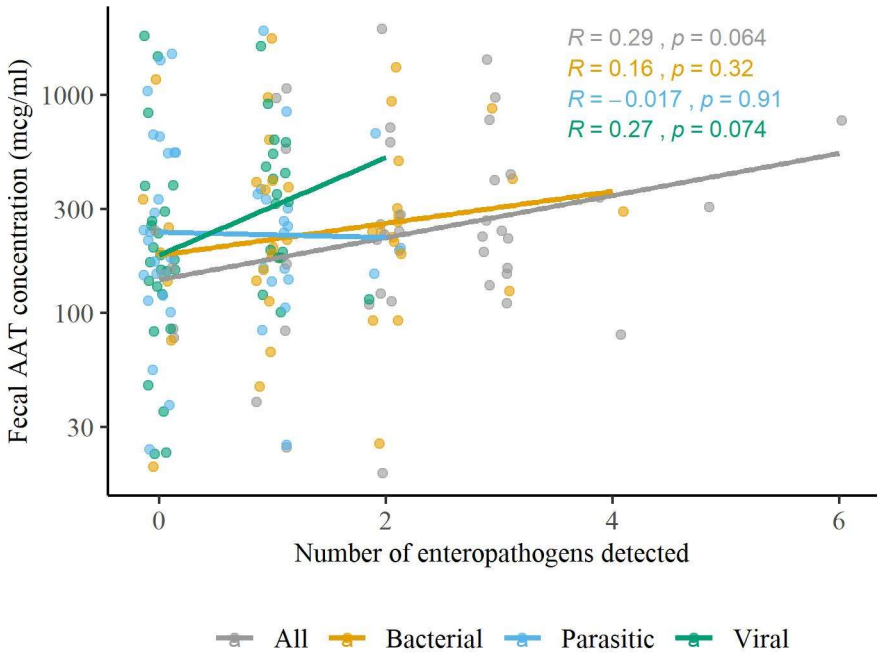
1. Tanzania Ministry of Health and Social Welfare/National Tuberculosis and Leprosy Programme. Manual for the Management of Tuberculosis and Leprosy, Sixth Edition, 2013 https://ntlp.go.tz/site/assets/files/1047/ntlp_manual_sixth_edition_2013.pdf
2. Tanzania Ministry of Health and Social Welfare/National Tuberculosis and Leprosy Programme. National Guidelines for the Management of Tuberculosis in Children. First Edition, 2012.
3. Tanzania Ministry of Health, Community Development, Gender, Elderly and Children/National Tuberculosis and Leprosy Programme. National Guidelines for the Management of Tuberculosis in Children. Third Edition, 2016. https://ntlp.go.tz/site/assets/files/1047/pdf__final_draft__ped_guideline_02_05_2017.pdf
4. Liu J, Gratz J, Amour C, et al. Optimization of Quantitative PCR Methods for Enteropathogen Detection. PLoS One 2016; **11**(6):e0158199.

Supplemental Figures

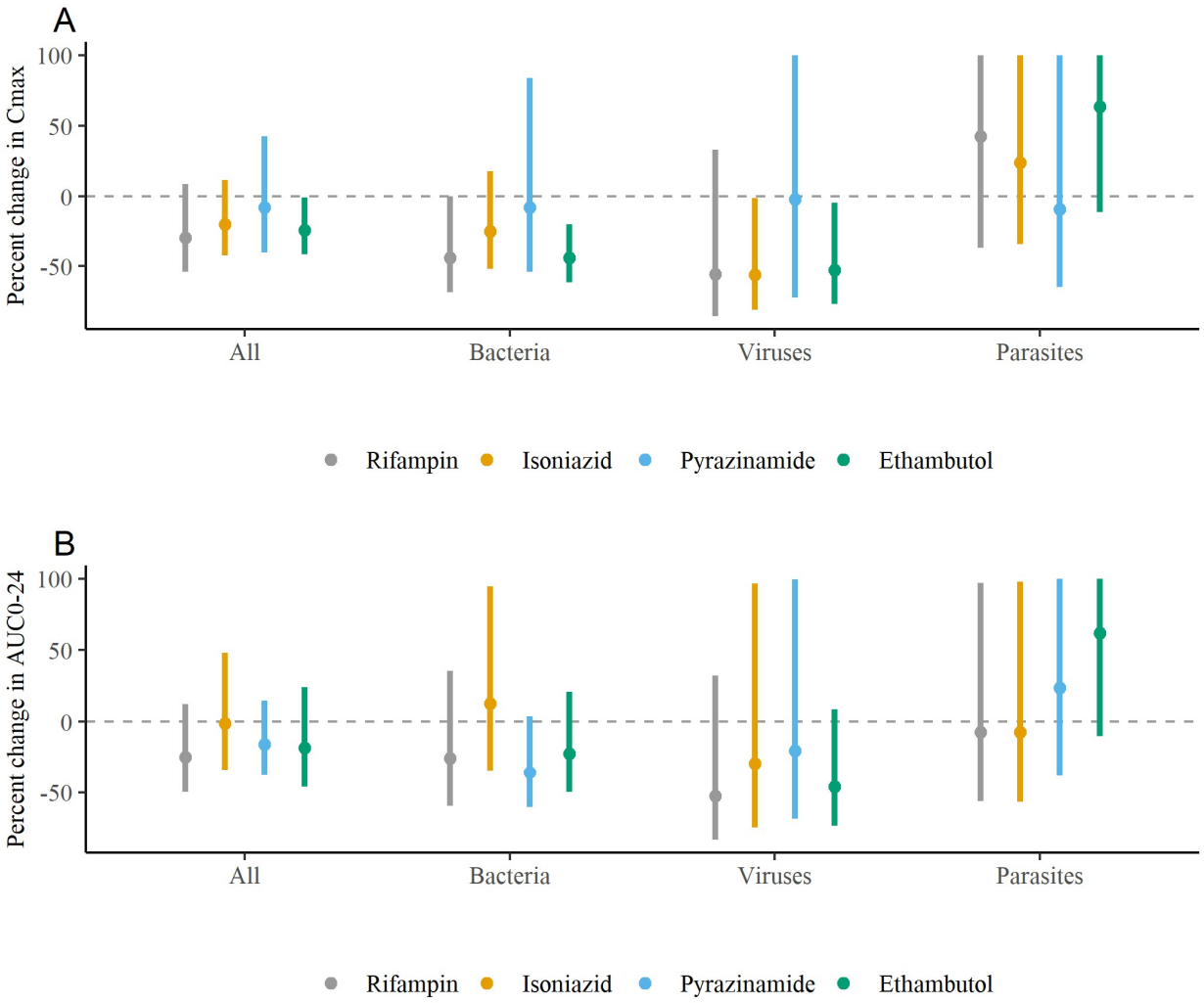
Supplemental figure 1. Scatterplot of fecal myeloperoxidase (MPO) concentration versus number of enteropathogens detected in stool.



Supplemental figure 2. Scatterplot of fecal alpha-1-antitrypsin (AAT) concentration versus number of enteropathogens detected in stool.

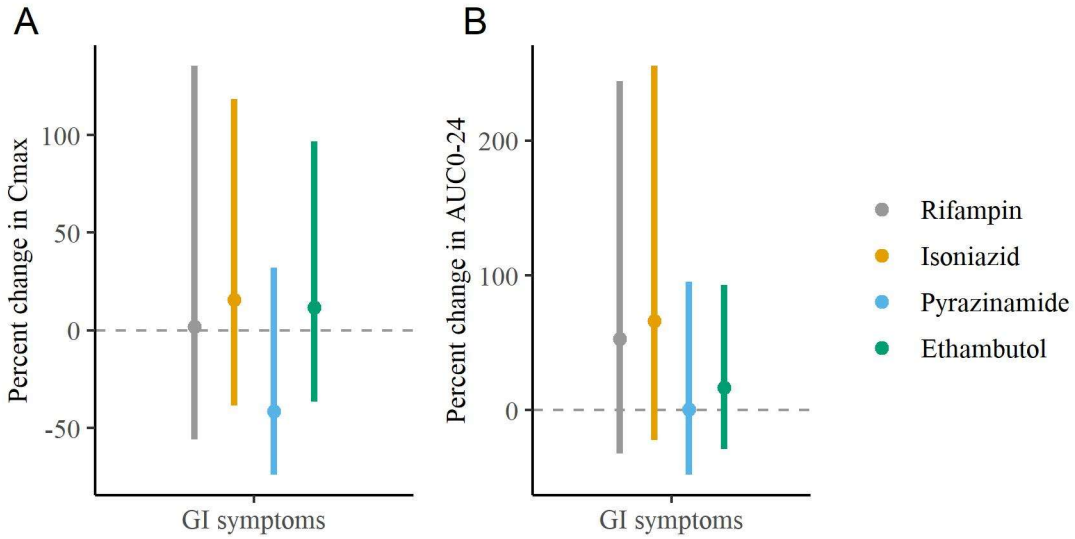


Supplemental figure 3. Combined effect of enteropathogen burden and presence of an abnormal fecal biomarker on peak serum drug concentration (C_{max}) (A) and area under the concentration curve (AUC_{0-24}) (B).



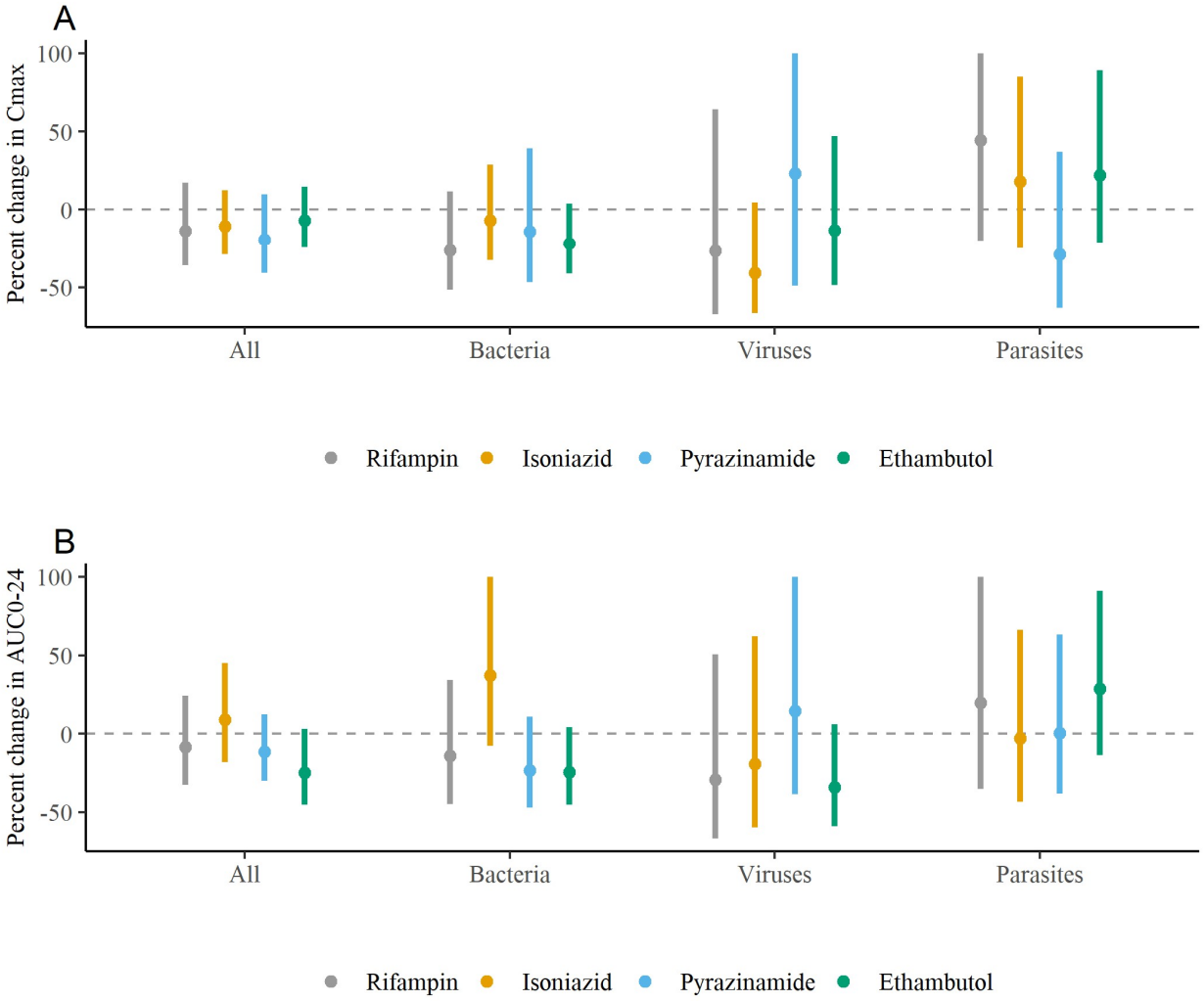
Log-C_{max} and log-AUC_{0-24} were modeled as functions of enteropathogen burden and the presence of either abnormal fecal myeloperoxidase (>2,000 ng/ml) or an abnormal fecal alpha-1-antitrypsin (>270 µg/ml). Estimates were back-transformed to calculate relative change in C_{max} or AUC_{0-24}. Estimates were adjusted for mg/kg drug dose, age, sex, and BMI z-score. 95% confidence intervals are shown and are truncated above 100%.

Supplemental figure 4. Effect of the presence of gastrointestinal (GI) symptoms on peak concentration (C_{max}) (A) and area under the concentration curve (AUC_{0-24}) (B).



Log-C_{max} and log-AUC_{0-24} were modeled as functions of enteropathogen burden without accounting for gastrointestinal symptoms or presence of abnormal fecal biomarkers. Estimates were back-transformed to calculate relative change in C_{max} or AUC_{0-24}. Estimates were adjusted for mg/kg drug dose, age, sex, and BMI z-score. 95% confidence intervals are shown.

Supplemental figure 5. Effect of enteropathogen burden on peak serum drug concentration (C_{max}) (A) and area under the concentration curve (AUC_{0-24}) (B).



Log-C_{max} and log-AUC_{0-24} were modeled as functions of enteropathogen burden. Effect size shown is the relative change in C_{max} or AUC_{0-24} associated with detection of an additional pathogen, without adjusting for gastrointestinal symptoms or fecal biomarkers. Estimates were adjusted for mg/kg drug dose, age, sex, and BMI z-score. 95% confidence intervals are shown and are truncated above 100%.

IRB-HSR PROTOCOL

Investigator Agreement

BY SIGNING THIS DOCUMENT, THE INVESTIGATOR CONFIRMS:

1. I am not currently debarred by the US FDA from involvement in clinical research studies.
2. I am not involved in any regulatory or misconduct litigation or investigation by the FDA.
3. That if this study involves any funding or resources from an outside source, or if you will be sharing data outside of UVA prior to publication that you will contact the Dean's office regarding the need for a contract and letter of indemnification. If it is determined that either a contract or letter of indemnification is needed, subjects cannot be enrolled until these documents are complete.
4. The proposed research project will be conducted by me or under my close supervision. It will be conducted in accordance with the protocol submitted to and approved by the IRB including any modifications, amendments or addendums submitted and approved by the IRB throughout the life of the protocol.
5. That no personnel will be allowed to work on this protocol until they have completed the IRB-HSR On-line training and the IRB-HSR has been notified.
6. That all personnel working on this protocol will follow all IRB-HSR Policies and Procedures as stated on the IRB-HSR Website http://www.virginia.edu/vprgs/irb/ and on the School of Medicine Clinical Trials Office Website: http://knowledgelink.healthsystem.virginia.edu/intranet/hes/cto/sops/sop_index.cfm
7. I will ensure that all those delegated tasks relating to this study, whether explicitly or implicitly, are capable through expertise, training , experience or credentialing to undertake those tasks.
8. I confirm that the implications of the study have been discussed with all Departments that might be affected by it and have obtained their agreement for the study to take place.
9. That no subjects will be recruited or entered under the protocol until the Investigator has received the signed IRB-HSR Approval form stating the protocol is open to enrollment
10. That any materials used to recruit subjects will be approved by the IRB-HSR prior to use.
11. That all subjects will sign a copy of the most current consent form that has a non-expired IRB-HSR approval stamp.
12. That any modifications of the protocol or consent form will not be initiated without prior written approval from the IRB-HSR, except when necessary to eliminate immediate hazards to the subjects.
13. Any significant findings that become known in the course of the research that might affect the willingness of subjects to enroll or to continue to take part, will be promptly reported to the IRB.
14. I will report immediately to the IRB any unanticipated problems involving risk to subjects or to others including adverse reactions to biologics, drugs or medical devices.
15. That any serious deviation from the protocol will be reported promptly to the Board in writing.
16. That any data breach will be reported to the IRB, the UVa Corporate Compliance and Privacy Office , UVa Police as applicable.
17. That the continuation status report for this protocol will be completed and returned within the time limit stated on the form.
18. That the IRB-HSR office will be notified within 30 days of a change in the Principal Investigator or of the closure of this study.

19. That a new PI will be assigned if the current PI will not be at UVA for an extended period of time. If the current PI is leaving UVa permanently, a new PI will be assigned PRIOR to the departure of the current PI.
20. All study team members will have access to the current protocol and other applicable documents such as the IRB-HSR Application, consent forms and Investigator Brochures.
21. Signed consent forms and other research records will be retained in a confidential manner. Records will be kept at least 6 years after completion of the study.
22. No data/specimens may be taken from UVa without a signed Material Transfer Agreement between OSP/SOM Grants and Contracts Office and the new institution. Original study files are considered institutional records and may not be transferred to another institution. I will notify my department administration regarding where the originals will be kept at UVa. The material transfer agreement will delineate what copies of data, health information and/or specimens may be taken outside of UVa. It will also approve which HIPAA identifiers may be taken outside of UVa with the health information or specimens.
23. If any member of study team leaves UVa, they are STRONGLY ENCOURAGED to use Exit Checklist found on IRB-HSR website at http://www.virginia.edu/provost/facultyexit.pdf.

The IRB reserves the right to terminate this study at any time if, in its opinion, (1) the risks of further experimentation are prohibitive, or (2) the above agreement is breached.

Investigators Experience

Scott K. Heysell, MD, MPH- Dr. Heysell is Assistant Professor of Medicine in the Division of Infectious Diseases and International Health at UVA. He has numerous international collaborations, including at the Siberia, Tanzania and Bangladesh sites within this study, and performed field research in tuberculosis. He is an expert in the pharmacotherapy for tuberculosis. He will serve as overall PI, responsible for the Pharmacotherapy aspects of the study.

Eric R. Houpt, MD- Dr. Houpt is Professor of Medicine in the Division of Infectious Diseases and International Health at UVA and Vice Chair for Research in the Department of Medicine. He has numerous international collaborations, including at all of the sites for this study, and is an expert in molecular diagnostics for infectious diseases. He will serve as overall co-PI with Dr. Heysell, responsible for the Diagnostics aspects of the study.

Tania Thomas, MD, MPH- Dr. Thomas is an Assistant Professor of Medicine in the Division of Infectious Diseases and International Health at UVA and an expert in Pediatric tuberculosis. Her main research sites are in Bangladesh and Tanzania, which will serve as enrollment sites for this study. She will serve as a Major Collaborator.

Chris C. Moore, MD- Dr. Moore is an Associate Professor of Medicine in the Division of Infectious Diseases and International Health at UVA and an expert in meningitis and sepsis in resource-limited settings. He has a longstanding research collaboration at the Uganda site for this study. He will serve as a Major Collaborator.

Jean Gratz - Ms. Gratz is an experienced microbiologist that has established research laboratories and trained laboratorians in resource limited settings across the globe. She lives part-time in Tanzania and will be responsible for onsite training in the laboratory protocol at all study sites.

Serhiy Vitko - Mr. Vitko is grants manager and project associate for this protocol with additional expertise in Russian translation which is important for one study site (Irkutsk, Siberia, Russian Federation). Mr. Vitko has travelled extensively with Drs. Heysell and Houpt in Siberia in the execution of prior clinical research projects in tuberculosis.

Esto Mduma, MPH - Mr. Mduma is Research Director at the Haydom Lutheran Hospital (HLH) in Tanzania and long-standing collaborator with Drs. Houpt and Thomas in Haydom. He will direct the activities at HLH.

Conrad Moozura, MD- Dr. Conrad Muzoora is PI of the Mbarara University Science and Technology (MUST) site. He is a faculty member in the Department of Internal Medicine at MUST and has worked with UVA/Moore for 5 years on sepsis and meningitis projects. He will oversee all aspects of the project, including management of the study team.

Stellah Mpagama, MD, PhD- Dr. Mpagama is PI of the Tanzania-Kibong'oto site. She has worked with UVA for the last 5 years on TB related projects at Kibong'oto National TB Hospital where she is Director of Research. She will oversee all aspects of the project, including management of study site team.

Blandina Mbaga, MD, PhD- Dr. Mbaga is director of Kilimanjaro Clinical Research Institute and will oversee the laboratory component for the Tanzania sites.

Sayera Banu, MD, PhD- Dr. Banu is PI of the Bangladesh site. She has worked with UVA previously on TB diagnostic projects and directs the Mycobacteriology Laboratory at icddr,b where she is a Senior Scientist. She will oversee all aspects of the project, including management of the study site team.

Oleg Ogarkov, PhD- Dr. Ogarkov is PI of the Siberia site. He has worked with UVA and Drs. Heysell and Houpt for the last 3 years. He directs the microbiology laboratory and the Scientific Centre of the Family Health and Human Reproduction Problems, Irkutsk, Russia and the laboratory department at the Irkutsk Regional TB-prevention Dispensary (site of patient enrollment).

Charles Peloquin, PharmD, PhD- Dr. Peloquin directs the Pharmacokinetics Laboratory at the University of Florida and is a world's expert in pharmacokinetic/dynamic analyses for anti-TB medications. He will serve as Major Collaborator with the responsibility of pharmacokinetic measurement and pharmacokinetic/dynamic data analyses.

Signatures

Principal Investigator

_____	_____	_____
Principal Investigator Signature	Principal Investigator Name Printed	Date

Department Chair

BY SIGNING THIS DOCUMENT THE DEPARTMENT CHAIR AGREES:

1. To work with the investigator and with the board as needed, to maintain compliance with this agreement.
2. That the Principal Investigator is qualified to perform this study.
3. That the protocol is scientifically relevant and sound.

_____	_____	_____
Department Chair or Designee Signature	Department Chair or Designee Name Printed	Date

Brief Summary/Abstract

More than 95% of all cases of tuberculosis (TB) occur in resource-limited settings, including more than 98% of all deaths [1]. Despite potentially curative therapy, deaths from TB outweigh any other single bacterial pathogen. The highest rates of mortality and greatest consumption of resources reside with severe forms of TB disease, including multidrug-resistant (MDR)-TB and the considerably neglected disease states of pediatric TB, TB meningitis and TB sepsis [2,3]. This protocol responds to a call to build capacity within an International Collaborations in Infectious Diseases Research (ICIDR) grant, and will unify diverse sites from unique TB-endemic settings to strengthen laboratory resources, develop personnel, and build clinical research infrastructure to study prospectively these severe forms. Each site within the proposed ICIDR TB Network (Tanzania- Kibong'oto, Tanzania-Haydom, Uganda, Bangladesh, and Siberia) has a productive research track record with the UVA team, and brings a thorough variety of TB disease states, comorbidities, and *M. tuberculosis* strain drug-resistance patterns. Among patients with the severe TB syndromes, we will measure drug concentrations for key anti-TB medications, perform quantitative susceptibility testing on the patient's *M. tuberculosis* isolate, and correlate these findings to TB treatment outcome. We hypothesize that pharmacokinetic thresholds will independently predict outcome, specifically area under the time-concentration curve (AUC)/ minimum inhibitory concentration (MIC). Threshold determination and association with treatment outcome will be by classification and regression tree analysis (CART). Additional exploratory and capacity building aspects include stool and urine studies for potential explanation of drug malabsorption, and deployment of molecular diagnostics platforms for correlates of MIC.

Background

1. Provide the scientific background, rationale and relevance of this project.

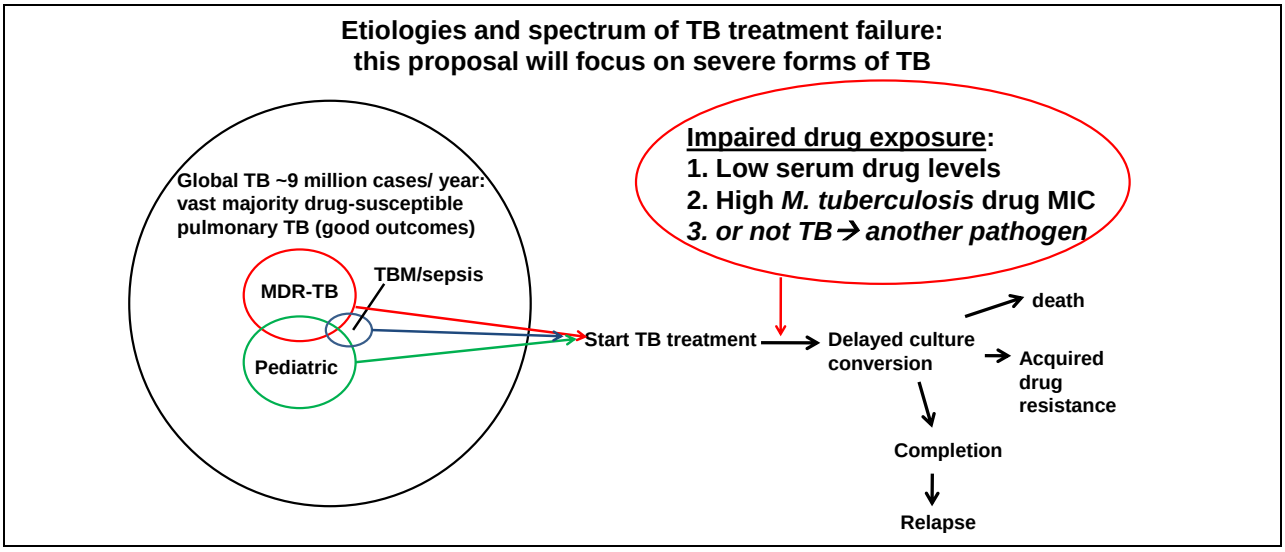
Mycobacterium tuberculosis (TB) is the leading cause of death from a curable infectious disease [1]. Drug-susceptible TB when caught early can be cured with >95% success. However, the highest rates of mortality and greatest consumption of resources reside with severe forms of TB disease, including multidrug-resistant (MDR)-TB and the considerably neglected disease states of pediatric TB, TB meningitis and TB sepsis [2,3]. Of the severe forms, multidrug-resistant (MDR)-TB has emerged as a legitimate threat to erode prior gains in global TB control [2, 3]. For example, at our study site in Irkutsk (Siberia, Russia), more than a quarter of all TB patients without prior treatment (no acquired drug-resistance) had MDR-TB, and half of those patients died during their hospitalization [4]. MDR-TB is defined as resistance to isoniazid and rifampin, the two most potent drugs of the typical 6 month "short" course regimen. One of the few means of overcoming the early mortality from MDR-TB is the rapid institution of 4 or more drugs to which the TB is susceptible [5]. However in most MDR-TB endemic settings, drug susceptibility testing (DST) is rarely available as a guide, since such testing requires a sophisticated biosafety environment and is so slow that often the patient with severe TB has since died. If one survives the early mortality, regimen durations extend to 20 months or more [6], outstretching the fragile resources of TB control programs in endemic countries. For example, at our study site in Dhaka, Bangladesh, ~100 patients are currently waiting and dying in a queue for admission. Meanwhile at our study site in Tanzania, Kibong'oto National TB Hospital, it takes a median of 131 days from diagnosis to initiation of treatment, again because of treatment duration and overall capacity constraints [7]. An optimized multidrug regimen for MDR-TB is desperately needed.

While MDR-TB drains budgets and sparks fear of contagion, other severe forms of disease simply kill patients. For example, pediatric TB is a sentinel event for ongoing community transmission and speaks poorly for many parts of the world where children <15 years old bear the highest proportion of MDR-TB [8]. The

diagnosis of pediatric TB is incredibly difficult as the low bacterial burden limits the ability to culture (and hence perform drug-susceptibility testing) and relies on a combination of poorly sensitive microbiology, clinical signs/symptoms, and radiography. We found that Tanzanian children diagnosed with pulmonary TB on purely clinical grounds had a significantly higher mortality (13.3%) compared to those who were positive for acid-fast bacilli by sputum microscopy (8.2%) [9]. Both rates are unacceptably high, and the higher rate in clinical diagnoses could have several explanations: late diagnosis, TB with poor outcome (perhaps due to insufficient dosing), TB with lack of drug-susceptibility testing (e.g., infection unknowingly with MDR-TB), or *not* TB with lack of detection of a non-TB pathogen. Many children with clinical diagnoses may have other etiologies, exposing the child to the wrong and potentially harmful treatment and obscuring interpretation of "TB" outcome.

The greatest mortality rate in TB disease occurs in the syndromes of TB meningitis and severe TB sepsis. A 43-year review of TB meningitis in Africa found a case fatality rate of 60% [11]. In Mbarara, Uganda, our final study site, we prospectively identified TB meningitis in 22% (32/145) of patients with clinically suspected meningitis and TB meningitis was associated with 28% in-hospital mortality and a 47% 30-day mortality [12]. TB is difficult to culture from cerebrospinal fluid (CSF) and such testing is usually unavailable in endemic settings, therefore like pediatric TB, diagnosis is based on a clinical algorithm and prone to similar misdiagnosis [13]. Even when TB meningitis is confirmed, a paucity of controlled trials and an incomplete understanding of the pharmacokinetics (PK) of anti-TB therapy complicate management. For instance, rifampin, critical to the early bactericidal action in non-CNS TB, poorly penetrates the blood-brain-barrier, and despite the evidence for its importance in TBM treatment, few studies have determined the means of optimized dosing and administration [14, 15]. Distinct from other forms of extrapulmonary TB, severe sepsis is an increasingly recognized cause of mortality from TB. In an analysis of 53 patients from the US, Canada, and Saudi Arabia with septic shock due to TB, the mortality rate was 79% (higher than other forms of sepsis [16]). In Mbarara, severe sepsis is a leading cause of death in hospitalized patients [17-19] and in a study of a sepsis treatment algorithm, TB was the predominant pathogen identified in blood (20% of 426 patients [19, 20]). Patients with TB bacteremia had a higher 30-day mortality (53% vs. 32%, $p<0.001$) than patients without TB bacteremia [18], and blood was often the only source of cultured TB and means of MDR-TB diagnosis [21]. However, despite the high mortality and recognition that variation in drug PK occurs in patients with critical illness (e.g., changes in volume of distribution, gut transit time, altered protein binding and clearance) [22-24] there are no available data regarding anti-TB PK in severe sepsis, as almost all PK studies involve ambulatory patients with pulmonary TB.

Hence, this observational cohort will focus on the most actionable etiologies of poor TB treatment outcome in the forms of TB with the highest mortality and public health expense:



Hypothesis to be Tested

Patients with AUC values for two or more drugs below a CART derived threshold will be significantly more likely to have a poor TB treatment outcome defined as death, microbiological failure, relapse or acquired drug resistance. AUC/MIC values will provide improved discrimination compared to AUC alone.

Study Design: Biomedical

1. **Will controls be used?** No.

2. **What is the study design?** Prospective cohort study.

3. **Does the study involve a placebo?** No.

Human Participants

Ages: all ages
Sex: Male and Female
Race: No racial exclusion

Subjects: see below

1. **Provide target # of subjects (at all sites) needed to complete protocol.**
   Tanzania/ Haydom: 50
   Tanzania/ Kibong'oto: 125
   Bangladesh: 175
   Uganda: 70
   Siberia: 145
   Total: 565

2. Describe expected rate of screen failure/ dropouts/withdrawals from all sites.

Tanzania/ Haydom: 15%
Tanzania/ Kibong'oto: 20%
Bangladesh: 20%
Uganda: 20%
Siberia: 25%

3. How many subjects will be enrolled at all sites?

Tanzania/ Haydom: 59
Tanzania/ Kibong'oto: 155
Bangladesh: 220
Uganda: 87
Siberia: 192
Total: 713

4. How many subjects will sign a consent form under this UVa protocol? 713.

Provide an estimated time line for the study.

Year 1: 25% enrolled
Year 2: 75% enrolled
Year 3: 100% enrolled
Year 4: follow-up, begin data cleaning
Year 5: analysis and publication

Inclusion/Exclusion Criteria

1. List the criteria for inclusion

Patients admitted to one of the study site hospitals with at least ONE of the following:

1) Clinical suspicion for TB in a child, as defined by NIH Consensus Case Definitions for TB research in children [25], and started on TB treatment
2) Clinical suspicion for TB meningitis, as defined by the International TB Meningitis Workshop Consensus Case Definitions for TB Meningitis [26]
3) Clinical suspicion for TB sepsis, as defined by the Uganda/PRISM-U definitions [27]
4) Microbiologic evidence of MDR-TB from a respiratory specimen within the past 6 months

2. List the criteria for exclusion

1) Pregnant women-self reported
2) Patient unable per treating physician discretion to undergo sample collection
3) Patient or representative/guardian unable to sign written informed consent
4) Patient unable to return for follow-up or be contacted by phone for follow-up

3. List any restrictions on use of other drugs or treatments. None.

Statistical Considerations

1. Is stratification/randomization involved? No.

2. What are the statistical considerations for the protocol?

Design:
A prospective observational cohort study design will be used to determine whether patients with severe forms of TB and AUC values for two or more drugs below a CART derived threshold will be significantly more likely to have a poor TB treatment outcome. In patients with a cultured *M. tuberculosis* isolate, AUC/MIC values will be compared to AUC alone.

Sites:
Data collection and follow-up will be harmonized across the study sites of Tanzania-Kibong'oto, Tanzania-Haydom, Uganda, Bangladesh and Siberia given the diversity of patient populations and *M. tuberculosis* drug-resistance patterns.

Definitions:
Primary Endpoint → final TB treatment outcome
Poor TB treatment outcome = death (from any cause), treatment failure (lack of sputum culture conversion to negative at 6 months or bacteriological reversion in the continuation phase for patients with MDR-TB), relapse or acquired drug resistance (two-fold increase in MIC or conversion from susceptible to resistant for any drug in the regimen).

Favorable TB treatment outcome = treatment completion and *neither* death, treatment failure, relapse nor acquired drug resistance.

Exposure → AUC or AUC/MIC values below threshold for two or more drugs in the patient's treatment regimen.
AUC = area under the time concentration curve, a measure of a patients cumulative circulating drug concentrations during a single dosing interval, performed for all drugs in the regimen
MIC = minimum inhibitory concentration, a quantitative measure of drug-susceptibility of the *M. tuberculosis* isolate, performed for all drugs in the regimen

Narrative assessment of objectives:
All enrolled subjects will have a detailed clinical assessment at study initiation, phlebotomy for pharmacokinetics to determine AUC for anti-TB drugs following initiation of therapy, quantiative susceptibility testing of the *M. tuberculosis* isolate for MIC, regular monitoring of clinical and microbiological parameters, and determination of the final TB treatment outcome (see schedule of procedures below). The study design, measured exposures and primary endpoint allow adequate sample size to answer the hypothesis, feasibility of enrollment and study activities, and completion of important secondary (exploratory) analyses in currently understudied TB disease states.

Interim analyses:
An interim analysis will be performed at 12 months to examine if determinants of sample size were similar to what was predicted at the study start, and if necessary, enrollment targets will correspondingly be adjusted.

Power/precision:
Given our prior work we have estimates of the primary TB treatment outcome and how that may vary across the severe TB diseases states. Similarly, we have estimates of the proportion in the total population with exposure (drug concentrations/ MIC) but for drug concentrations at the pharmacokinetic peak only which is a correlate of AUC for the drugs to be analyzed. The most comparable study to date enrolled adult patients with drug-susceptible pulmonary TB (not the severe category of TB studied here) but examined the impact of AUC only on treatment outcomes (not AUC/MIC) [28]. Hence, this is the first study to examine rigorously the impact of AUC/MIC in the proposed study populations. Yet using our prior data and extrapolating from the study in drug-susceptible pulmonary TB we can provide adequate estimates of the ratio of exposed/unexposed and the proportion of exposed and unexposed with the outcome. We have the greatest understanding of these estimates for patients with MDR-TB that will make up the majority of the study population.

3. Provide a justification for the sample size used in this protocol.

We estimate that for patients with MDR-TB, the ratio of unexposed (AUC/MIC values below threshold for one or no drug) to exposed (AUC/MIC values below threshold for two or more drugs) to be 3.0. Outcomes will vary across sites but it is anticipated that overall, 25% of unexposed will have poor TB treatment outcome. A logistic regression model will be used to estimate the effect of exposure, based on previously estimated thresholds, on outcome, adjusting for site differences. With the sample sizes given from the 5 sites, the Wald test has 80% power, with a 2-sided significance level of 5% for an odds ratio of 1.9. This corresponds to 39% of exposed patients having a poor TB outcome. The odds ratio of 1.9 is well within the effects shown in the other study of AUC and TB treatment outcomes in drug-susceptible pulmonary TB (see discussion of analyses below). Secondary analyses will add site by exposure interaction terms to the model to test whether the effect of exposure varies across sites.

An interim analysis will occur when half of the subjects have been enrolled. This interim analysis will be conducted to examine data quality and timeliness of data submission, and to provide early estimates of the predictive ability of the AUC/MIC thresholds.

It is anticipated that the study sites in Bangladesh, Tanzania/Kibong'oto and Siberia will contribute the bulk of patients with MDR-TB. Thus the accrual targets for MDR-TB at those sites, and the additional proportion enrolled to account for withdrawal and loss to follow-up, will allow additional comparisons across sites for this particular form of severe TB disease. Given the relative absence of AUC/MIC data in the other severe forms of TB disease, accrual goals at each site for these diseases (TB sepsis, TB meningitis and pediatric TB) are based on feasibility. As outlined above, we expect to complete enrollment by the beginning of Year 3, but patients will be followed every 6 months through Year 5.

4. What is your plan for primary variable analysis?

AUC values will be interpreted using noncompartmental, compartmental and/or population PK techniques appropriate for individual drugs. The robustness of the pharmacokinetic sampling strategy will be calculated by applying optimal sampling theory (D-optimality design) to determine if bias had been adequately minimized. AUC values and AUC/MIC values (when applicable) will then be analyzed among other clinical parameters against the binary treatment outcome by classification and regression tree (CART) analytics. CART utilizes nonlinear statistical methodology that is likely superior for systems such as TB pharmacokinetics and TB disease states given the purportedly better characterization of higher-order complexity among diverse data elements [28, 29]. It is expected that CART derived thresholds for AUC/MIC predictive of outcome will be defined for 3 drugs within the multidrug TB regimen. Odds ratios (and 95% confidence intervals) for poor treatment outcome will be determined for patients with none, 1, 2 or 3 drugs below the CART derived threshold, and we estimate that 2 or more drugs below the threshold will significantly associate with poor outcome. We recognize that using logistic regression based on thresholds derived the CART analysis can give overly-optimistic estimates of the predictive power of AUC/MIC thresholds for predicting outcome. We intend to use cross-validation and bootstrap methods [30, 31] to 'correct for optimism' in the logistic regression. With the bootstarp method, we can replicate the entire process, from resampling estimates of the thresholds through to logistic regression.

5. What is your plan for secondary variable analysis?

AUC/MIC parameters in the non-MDR-TB patients may not be predictive of outcome given feasibility of enrollment for these disease states. Nevertheless, highly valuable information will be obtained for the field and for designing future study. In these subsets, for instance in patients enrolled with TB sepsis, AUC/MIC values will be compared to the expected ranges in drug-susceptible pulmonary TB and expressed as both a population value and at the individual level (proportion of patients below the expected range for each drug).

6. Have you been working with a statistician in designing this protocol? Yes.

IF YES, what is their name?

Mark Conaway, PhD - Professor, UVA PBHS Public Health Sciences.

7. Will data from multiple sites be combined during analysis? Yes.

7(a). Does the study involve randomization? No.

7(b). Has the sample size calculation considered the variation among sites?

Yes. The power calculations were based on a logistic regression model that allowed for variation across sites.

7(c). When combining the data from multiple sites to assess the study results, is the effect of the treatment to be tested (or the association to be tested) assumed to be the same across sites or vary among sites? What is the modelling strategy?

Yes. Logistic regression models with a common effect for the AUC/MIC thresholds will be fit initially; site by threshold terms will be added to test for differences in the exposure effect across sites. Resampling (bootstrap and premutation tests) methods will be used to estimate and test differences in the CART-derived thresholds across sites.

7(d). Is there a common protocol used in all sites?

Yes.

Information from Outside Institution

1. **List the names of outside institutions that will be supplying data and/or specimens for this study.**
   1) Kibong'oto National TB Hospital and the Kilimanjaro Clinical Research Institute, Moshi, Tanzania
   2) Haydom Lutheran Hospital, Haydom, Tanzania
   3) International Centre for Diarrheal Diseases Research and the National Institute for Diseases of the Chest Hospital, Dhaka, Bangladesh
   4) Scientific Centre for Family Health and Reproductive Problems and Irkutsk Tuberculosis Referral Hospital, Irkutsk, Russian Federation
   5) Mbarara University Science Technology and Mbarara Regional Referral Hospital, Mbarara, Uganda
   6) University of Florida, Gainesville, Florida

2. **Describe the type of information you will receive from each site.**
   1. De-identified and coded clinical data
   2. Specimens

3. Does the outside institution have an IRB?

Yes. All institutes have an IRB (the Tanzanian sites report to a single IRB, the National Institute of Medical Research for Tanzania).

Biomedical Research

1. What will be done in this protocol?

Subjects will be recruited by medical officer review of new admissions to the TB hospitals at the study sites- Kibong'oto National TB Hospital (Tanzania), Haydom Lutheran Hospital (Tanzania), Irkutsk Regional Clinical Tuberculosis Hospital (Siberia/Russian Federation), National Institute of Diseases of the Chest Hospital (Bangladesh), ICDDRB Hospital (Bangladesh), Mbarara Regional Referral Hospital (Uganda).

All eligible subjects will be consented in their own language per GCP standards using local/UVA IRB approved forms. All enrolled subjects at each of the study sites are assigned individual study ID#s that are used for all forms.

At enrollment the following data will be collected from chart review, TB program registry and interview: demographics, prior TB history including precise prior TB treatment regimens, anatomic site of TB disease, detailed medical comorbidities, report of chest radiograph per our standardized scoring system [32], Karnofsky score and baseline laboratory values. All data collection will initially be performed on standardized case report forms, then managed by onsite data managers using the Multi-Schema Information Capture

(MuSIC) framework across sites. All case report forms will be stored in locked file cabinets within a locked research office at the study site. Computers used for data management will be password protected, locked within the research office and accessible only to the onsite study investigators.

All procedures for baseline data collection, respiratory specimen collection, phlebotomy, urine and stool collection, saliva collection, and treatment outcomes measurement will be standardized across each enrollment site. Leftover specimens of cerebrospinal fluid will be collected in the subset of subjects with TB meningitis if performed as part of routine clinical assessment of treatment response (see summary Table of activities). It is standard of care to perform repeat cerebrospinal fluid analysis following treatment initiation at Irkutsk Tuberculosis Referral Hospital and Mbarara National Referral Hospital, the study sites that will enroll patients with TB meningitis, and a single sample can be used from the time of estimated peak concentration. If a respiratory specimen is unable to be collected for mycobacterial culture and drug-susceptibility testing, a pretreatment *M. tuberculosis* isolate that has been cultured previously for routine clinical purposes will be used for drug-susceptibility testing.

Phlebotomy for full pharmacokinetic sampling will be performed 2 weeks after enrollment (to allow steady-state of anti-TB meds). All medication will be directly administered in the fasting state and observed by nursing staff. All anti-TB medications are given as a morning or split morning dose. The study will not prescribe anti-TB medications but will document what medications and dosages are given per routine care. Venous blood will be drawn at 1, 2, 4, 6 and 8 hours after medication administration with attempt by single venipuncture for peripheral IV insertion. Such sampling allows for adequate calculation of Cmax and AUC. A maximum of 7 ml will be obtained in heparinized tubes at each draw as up to 4 drugs will be required to be assayed for determination of drug concentration within a multidrug anti-TB regimen. For pediatric patients, the timing of blood draws will be limited to 1, 2 and 4 hours with a maximum of 5 mL drawn at each time point but not to exceed 3 mL/kg of bodyweight. A single venipuncture will be performed at 2 hours after medication administration at 4, 8 and 24 weeks after enrollment, to compare spot samples of estimated C_{max} at different treatment durations to AUC. Blood will be immediately centrifuged onsite at the enrollment hospital and plasma stored at -80^{o}C for batch shipment to the Infectious Diseases PK Laboratory at the University of Florida, where established protocols for testing all anti-TB drugs are operational. Protocols include CLIA-validated HPLC-UV, -FL, gas chromatography and tandem mass spectrometry assays. The leftover cerebrospinal fluid from patients with TB meningitis will also be similarly stored at -80^{o}C and shipped in batch to the University of Florida and analyzed as for plasma pharmacokinetics.

Saliva (2 ml) will be collected at the time of the first pharmacokinetic blood draw. This sample will be tested by polymerase chain reaction or direct DNA sequencing for human DNA sequences known to be associated with drug metabolism, drug bioavailability and other relevant biomarkers.

The respiratory specimen collected at enrollment will be cultured at the onsite laboratories, and tested for alternative pathogens. Cultured mycobacterial growth will be speciated by molecular tests to determine if *M. tuberculosis* complex. All *M. tuberculosis* isolates will undergo quantitative MIC testing by a Sensititre MYCOTB plate (TREK Diagnostics) and molecular testing for drug-resistant mutations. In patients able to produce a respiratory specimen at 8 weeks and 24 weeks after enrollment, this specimen will be cultured on solid and liquid media to determine culture conversion. 8 week culture conversion has been a clinical parameter associated with treatment outcome [33, 34], while 24 week culture conversion will be used to document if microbiological failure (a component of overall treatment outcome). Patients will be contacted every 6 months thereafter for an aim of 2 years after enrollment. Attempts will be made to interview patients in person or over the phone which will include a symptom screen. P**atients with TB symptoms will be referred for repeat respiratory specimen collection at mycobacterial culture.** Specimen found to be positive for *M.*

tuberculosis testing will undergo drug-susceptibility testing for determination of acquired drug resistance, as well as molecular typing to determine if different from the patient's original *M. tuberculosis* strain cultured at enrollment. Additionally, stool, urine, blood and cerebrospinal fluid will be tested for *M. tuberculosis* complex, markers of TB disease or malabsorption, and other pathogens.

All patients started on TB treatment at all study sites are traced by governmental TB programs for outcomes per routine. These records will also be reviewed to supplement the follow-up case report forms and assure accurate reporting of the final treatment outcome.

Procedure	**Screen**	**Baseline**	**Week 2***	**Week 4**	**Week 8**	**Week 24**	**Week 24-96**
Informed Consent	X						
Eligibility CRF		X					
Initial clinical CRF		X					
Chest x-ray report CRF		X				X	
Medications list CRF		X		X		X	
Audiometry report CRF (MDR-TB only)		X			X	X	
Urine collection (TB sepsis only`)			X				
Stool collection (pediatric TB and TB sepsis only)		X					
Leftover CSF collection			X				
Respiratory specimen collection		X			X	X	X (only if new TB symptoms)
Phlebotomy		X, single draw only	X, full PK sampling	X, single draw only	X, single draw only	X, single draw only	
Saliva collection		X					
TB treatment status CRF				X		X	X

*After treatment initiation.

2. List the procedures, in bullet form, that will be done for <u>RESEARCH PURPOSES</u> as stipulated in this protocol.

- phlebotomy within age appropriate minimal risk volumes
- respiratory specimen collection per age appropriate local standards of care
- stool collection
- urine collection
- leftover cerebrospinal fluid collection
- saliva collection
- patient interview
- medical chart review

3. Will you be using data/specimens in this study that were collected previously, with the use of a research consent form, from another research study? No.

4. Will any of the procedures listed in item # 2 have the potential to identify an incidental finding? This includes ALL procedures, assessments and evaluations that are being done for RESEARCH PURPOSES that may or may not be considered investigational. No.

5. Do any of the procedures listed above, under question # 2, utilize any imaging procedures for RESEARCH PURPOSES?

No. The chest x-rays are not performed for research purposes. A data collection form is used to document the results of a chest x-ray, if done for clinical purposes.

6. Will you be using viable embryos? No.

7. **Will you be using embryonic stem cells?** No.

8. **Are any aspects of the study kept secret from the participants?** No.

9. **Is any deception used in the study?** No.

10. If this protocol involves study treatment, explain how a subject will be transitioned from study treatment when they have completed their participation in the study. N/A.

Genetic Research

Background

1. Briefly describe the nature and purpose of the genetic research (what will be tested and how):
Answer/Response: This study will use clinical and related phenotypic data and saliva samples to identify and characterize genetic and molecular biological markers that will enrich our understanding of the biological basis of an individual's response to anti-TB drugs.

2. Could any genetic findings affect current treatment or therapy?
Answer/Response: No

Risks of Genetic Research

INSTRUCTIONS: Most genetic risk is probably future risk. It may be difficult now to anticipate confidentiality risks that participants may face one, five or ten years from now by being in this study at this time because the technology is not yet developed. In the future, it is possible that genetic testing results will be used more broadly by employers or insurers or considered by them. Since it is difficult to assess that risk now, participants should be provided with information that informs them of that uncertainty and the possibility that risk not present now may exist in the future. Sometimes the actual study will be important in determining the future

uses of such testing; in that case, provisions should be made to inform participants of any risks that become more apparent as the study progresses.

Answer/Response:

1. Risks of Accidental Disclosure/Loss of Confidentiality

INSTRUCTIONS: Many risks associated with genetic research are related to breaches in confidentiality. You should consider the mechanisms through which breaches might occur and the consequences of those breaches. Risk is related to the amount of data stored about a subject, the security of the data storage, the more likely linkages, and the seriousness of any condition related to the data.
Where the genetic study is linked to an already diagnosed disease, the risk to the subject may be minimal, but there may still be some significant risk to the family.

1.a. If there were an accidental disclosure of this research data, could it affect either the subject or the subject's family member(s)?

Answer/Response: No

►**IF YES, explain how:**
Answer/Response:

1.b. What data will you be keeping about a subject?

Examples: genetic results, clinical data related to the results, etc.

Answer/Response: Clinical data, laboratory data and genetic results will be linked and coded with the identifiers. The key to the codes kept locked in the local PI's office.

1.c. Where are you keeping this data and/or specimens?

Examples: central registry, central repository, data on excel spreadsheet maintained by study team

Answer/Response: All specimens and test results will be coded and stored separately from identifying information. This approach will help ensure that only the on-site study researchers will be able to identify subjects as the donor of these specimens. Genetic data will be stored in the electronic database.

1.d. Are there any documented correlations or associations that might be outside the study?

Examples: a study focusing on correlations between APOE-4 and brain trauma may reveal information about a participant's risk for early-onset Alzheimer's Disease even though that information is not part of the actual study.

Answer/Response: No

2. Social risks

INSTRUCTIONS: Misconceptions are often an important source of potential discrimination. Recent studies have shown that employers often fail to distinguish between having a genetic mutation and the possibility of becoming symptomatic with a disease.

Examples of types of social risks: health insurance, life insurance, disability insurance, employment, stigmatization, stress upon family relationships, change in reproduction plans, immigration status, forensic implications, and mistaken paternity. While we have federal and state legislation that protects some of this information, it does not cover many types of insurance, and data show that even with it, some discrimination still occurs.
Keep in mind that these risks may vary; a condition that implicates disability insurance may have a minimal impact on life insurance.

Answer/Response:

2.a. If there were a deliberate or accidental disclosure of the results or associated data from this research, could an insurer or employer think that it would affect the insurability or employability of the subject?

INSTRUCTIONS: Do not consider any legal restrictions on use of the information

Example, if a long-term care insurer has received information about a subject's APOE4 status, the status would affect the subject's insurability.

Answer/Response: No

2.b. If there were a deliberate or an accidental disclosure of the results or associated data from this research, could it affect reproductive plans of the subject or the subject's family member(s)?

Answer/Response: No

►**IF YES, explain how:**
Answer/Response:

2.c. If there were a deliberate or an accidental disclosure of the results or associated data from this research, could it stigmatize the subject?

Examples: alcoholism, drug abuse, gender identity issues, dementia, etc.

Answer/Response: No

►**IF YES, explain how:**
Answer/Response:

3. Psychological risks

Example: impact of results, impact of disease knowledge without treatment, disclosure of vague or uncertain results, stress related to other family members

3.a. If there were a deliberate or an accidental disclosure of the results or associated data from this research, could this cause psychological stress to the subject or a family member (include rational and irrational reactions)?

Example, if a child is diagnosed with a genetic condition, might a parent feel responsibility or guilt?

Answer/Response: No

4. Harm to the community

4.a. If your study involves an ethnic or cultural group, will the results affect that community?

Answer/Response: No

►**IF YES, explain the risks:**

Example: could the genetic information be used to cause a group or community of people to be vulnerable to discrimination based on actual or perceived associations, e.g. Ashkenazy Jews and the BRCA genes, or alcoholism or other addictions within ethnic or cultural groups?

Where a study may raise community risk, it may be a good idea to conduct focus group discussions with community representatives before the protocol is finalized.

Answer/Response:

4.b. How will the risks listed above be minimized?

Answer/Response:

4.c. How will these risks be communicated to participants?

Example: subjects will be notified of the risks during the consenting process

Answer/Response:

Information Accompanying Specimens or Data to be Used for Genetic Research

1. **What information will be on the label of the specimen to be used for genetic research?**

INSTRUCIONS: The IRB STRONGLY advises that you do not include HIPAA identifiers such as name, medical record number, subject initials on the label. If HIPAA identifiers will be included- you must provide a STRONG justification for this procedure.

Answer/Response: When any specimen or DNA/RNA extract is transferred from field site to a referral lab, the specimen will be coded with a sample ID (SID) number. The referral lab cannot subsequently access or obtain direct or indirect identifiers that are linked to the subjects as the linked code with identifiers is kept with the local investigators where the specimens were collected (e.g. Tanz, Uganda, etc.) and will not be transferred outside those location.

2. **What information will be "linked to" or will accompany the specimen to be used for genetic research?**

Examples: type of clinical information, type of demographic data, HIPAA identifiers such as name, Medical Record Number

Answer/Response: sample ID (SID) number

3. **If identifiers will be linked to specimens/ data, when will the identifiers be destroyed?**

__X___ NA- No identifiers
_____ After specimen is linked to clinical data but before genetic analysis is completed.
_____ After specimen is linked to clinical data and immediately after the genetic analysis for the individual participant is completed.
_____ After specimen is linked to clinical data and immediately after the genetic analysis for all participants is completed

_____ Link to identifiers will not be destroyed
_____ Other : Specify Answer/Response:

Confidentiality and Collection/Storage of Specimens to be Used for Genetic Research

1. **Will any information/ the consent form/ results regarding genetic research be placed in the participant's medical record?**
   Answer/Response: No

2. **How much material (e.g. blood, tissue) will be collected for genetic research and how will it be collected?**
   Answer/Response: Saliva samples – 2 milliliters

3. **Who will be responsible for storing the specimens for genetic research?**

Examples: sponsor, UVa PI, tissue bank/procurement facility, tissue bank outside of UVa?

   Answer/Response: Local investigators where the specimens were collected (e.g. Tanz, Uganda, etc.) and will not be transferred outside those location. The local investigators will keep the specimens stored in a restricted access freezer until DNA is tested.

4. **If stored at UVa-where will the specimens to be used for genetic research be stored?**

Examples: a refrigerator/freezer in a lab, a room-provide room number, or specific location To protect confidentiality, whenever possible, you should consider using a central facility/repository such as the UVa Biorepository and Tissue Research Facility.

   Answer/Response: Center for Public Health Genomics, PBHS Public Health Sciences Admin (Dr. Steven Rich)

5. **Will another research institution or entity outside of UVa ever have control over the specimens?**
   Answer/Response: No

   ►**IF YES, list the name of outside institution/entity.**
   Answer/Response:

6. **List the information that will be on the specimen label when the specimen is sent outside of UVa.**
   Answer/Response: sample ID (SID) number

7. **Will any additional information be sent with the sample?**

Examples: clinical information, HIPAA identifiers located on a separate piece of paper/ computer file

   Answer/Response: No

   ►**IF YES, list what will be sent.**
   Answer/Response:

Note to Study Team: If you plan to ship specimens outside of UVa, personnel performing this function must have taken the appropriate training from the Department of Transportation. Contact SOM CTO for training information.

Note to IRB Staff: If the information sent outside of UVa with the specimen meets the criteria of "Identifiable" and the study does not have a consent form- the disclosure would require Tracking under HIPAA regulations. If it meets the criteria of a Limited Data Set, a Data Use Agreement will be required.

8. **Can participants withdraw their specimens or request that they be destroyed?**

The answer to this question must be YES unless the specimens are stripped of all HIPAA identifiers.

Answer/Response: No

Third Party Concerns

1. **Will family members be directly involved in the research?**

Answer/Response: YES, parents/guardians of children enrolled in protocol.

►IF YES, how and by whom (*e.g., an investigator, the participant, a support group)* will those family members be recruited?

Answer/Response: By study team at time of enrollment

►IF NO, does this study have any implications for the participant's family members?

Answer/Response:

►IF YES, will that information be shared with relevant family members?

Answer/Response:

Genetic Research Results Not Disclosed to Subjects

1. **Briefly describe the nature and purpose of the genetic research (what will be tested and how).**

Answer/Response: This study will use clinical and related phenotypic data and saliva samples to identify and characterize genetic and molecular biological markers that will enrich our understanding of the biological basis of an individual's response to anti-TB drugs.

2. **Why will you not disclose genetic research results to subjects?**

Answer/Response: Testing will not be performed in real time, but will be batched for analysis at a later date

3. **If future research yields results that are clinically meaningful or significant, would those results be disclosed to the participant? Why or why not?**

Answer/Response: No, the genetic information will not be generated using FDA approved clinical tests.

4. **Even if results may not be clinically valid (*recognized by FDA or generally recognized by practitioners in the field as established*), might they affect a subject's clinical care?**

Answer/Response: No

►IF YES, how?

Answer/Response:

Specimens

Specimen Information

1. Describe the type of specimen to be used:

- Respiratory secretions (eg. sputum, leftover gastric aspirate).
- Leftover cerebrospinal fluid.
- Blood
- Urine
- Stool
- *M. tuberculosis* cultured organism.
- *M. tuberculosis* DNA.

2. Will the specimen be obtained BEFORE a subject has signed a consent form? No.

3. Will you be using discarded specimens? Yes.

►**IF YES, do you confirm that it will be obtained either from pathology, a clinical lab or the UVA Biorepository & Tissue Research Facility (BTRF)?**No.

►**IF you will not obtain the specimen from the sources listed above, describe the process for obtaining the discarded tissue.**
Residual volume of cerebrospinal fluid collected on enrolled patients for clinical purposes will be obtained directly from the clinical laboratory of the study sites for labeling with study ID # and storage at -80^{o}C.

Answer the following two questions as it pertains to ALL blood being drawn for this study.

►**IF NO, where will blood be drawn?**
__X__ in a clinical setting

►**IF NO, who will draw the blood?**
_____ a member of the study team who is an individual licensed to practice medicine or osteopathy, a nurse practitioner, or a physician assistant employed by UVa School of Medicine
__X__a member of the study team who is a person trained to draw blood by an individual licensed to practice medicine or osteopathy, a nurse practitioner, or a physician assistant employed by UVa. *Written documentation of training will be kept in research files. Individual also has current training in handling of blood borne pathogens*

►**IF NO, and taking a blood sample, will blood be taken more than 2 times/week?**No.

►**IF NO, and taking a blood sample, check the option(s) below which match the subject population.**
_____ Healthy, non-pregnant adults who weigh at least 110 pounds.
_____ Amount will NOT exceed 550 cc in an 8 week period.

_____ Amount to exceed 550 cc in an 8 week period.
__X__ Non-healthy or pregnant adults and/or children.
__X__ Amount will NOT exceed the lesser of 50ml or 3 ml/kg in an 8 week period.
_____ Amount will exceed the lesser of 50 ml or 3 ml/kg in an 8 week period.

Specimen Labeling

1. What information/ HIPAA identifiers will be on the specimen label when it is given to the study team (from clinical labs or other source outside the study team) and/or what information will you put on the specimen?

Subject study ID#, date of collection, time of collection.

2. If the specimen is given to the study team with information on the label will you delete any of the information on the specimen label?

No, the specimen will not be given to the study team with any other information.

3. Will any additional data be linked to the specimen by way of a code?

No.

4. Will the analysis on the specimen be done soon (within 24 hours) after it is collected?

For respiratory specimens, yes, as those specimens will be immediately set up for mycobacterial culture.

►**IF NO, where will the specimen be stored until analysis is done?**

For other specimens not immediately processed, the specimen will be stored in a -80^{o}C freezer that is within a locked repository of the onsite research laboratory.

Specimen Shipping

1. Do you plan to ship any specimens outside of UVA? No.

Data and Safety Monitoring Plan

1. Definition:

1.1 How will you define adverse events (AE) for this study?

__X__ Other: An adverse event will be considered any undesirable sign, symptom or medical or psychological condition **even if the event is not considered to be related** which occurs within 24 hours of specimen collection (blood, sputum, stool, urine).

1.2 How will you define serious adverse events?

__X__ A serious adverse event will be considered any undesirable sign, symptom, or medical condition which is fatal, is life-threatening, requires or prolongs inpatient hospitalization, results in persistent or significant disability/incapacity, constitutes a

congenital anomaly or birth defect, is medically significant and which the investigator regards as serious based on appropriate medical judgment. An important medical event is any AE that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions of SAEs.

1.3 What is the definition of an <u>unanticipated problem?</u>

An unanticipated problem is any event, experience that meets ALL 3 criteria below:

- Is unexpected in terms of nature, severity or frequency given the research procedures that are described in the protocol-related documents AND in the characteristics of the subject population being studies
- Related or possibly related to participation in research. This means that there is a reasonable possibility that the incident may have been caused by the procedures involved in the research study.
- The incident suggests that the research placed the subject or others at greater risk of harm than was previously known or recognized OR results in actual harm to the subject or others

1.4 What are the definitions of a protocol violation and/or noncompliance?

A **protocol violation** is defined as any change, deviation, or departure from the study design or procedures of research project that is NOT approved by the IRB-HSR prior to its initiation or implementation. Protocol violations may be major or minor violations.

Noncompliance can be a protocol violation OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulation**s**. Noncompliance may be serious or continuing.

1.5 If pregnancy occurs how will this information be managed?

__X__ Other: This study does not intend to enroll pregnant women. If a woman becomes pregnant during this observational study, it should not affect the study relate d procedures unless the pregnancy/related conditions meet the exclusion criterion #2 (patient unable per treating physician discretion to undergo sample collection).

1.6 What is the definition of a Protocol Enrollment Exception?

__X__ NA- No outside sponsor

1.7 What is the definition of a data breach?

A data breach is defined in the HITECH Act (43 USC 17932) as an unauthorized acquisition, access, or use of protected health information (PHI) that compromises the security or privacy of such information.

2. Identified risks and plans to minimize risk

2.1 What risks are <u>expected</u> due to the intervention in this protocol?

Expected Risks related to study participation.	**Frequency**
Risk related to **phlebotomy** include pain, bleeding, bruising or infection at site	____ Occurs frequently ____ Occurs infrequently __X__ Occurs rarely ____ Frequency unknown
Violation of subject's privacy and confidentiality	Minimized due to the requirements of the privacy plan in this protocol

2.2 List by bullet format a summary of safety tests/procedures/observations to be performed that will minimize risks to participants:

- Screening eligibility forms will be completed prior to full procedures.
- Phlebotomy will be performed by trained staff and participants will be observed after the procedure for possible adverse outcomes.
- Other specimen collection techniques will be performed per local standard of care.

2.3 Under what criteria would an INDIVIDUAL SUBJECT'S study treatment or study participation be stopped or modified

__X__ At subject, PI or sponsor's request.

2.4 Under what criteria would THE ENTIRE STUDY need to be stopped.

__X__ Per IRB, PI, DSMB, or sponsor discretion.

2.5 What are the criteria for breaking the blind/mask?

__X__ NA – Not blinded/masked.

2.6 How will subject withdrawals/dropouts be reported to the IRB prior to study completion?

__X__ IRB-HSR continuation status form

3. Adverse Event / Unanticipated Problem Recording and Reporting

3.1 Will all adverse events, as defined in section 1.1, be collected/recorded? No

►IF NO, what criteria will be used?

_____ Only adverse events deemed related/possibly related to study.

_____ Only adverse events that are deemed serious.

__X__ Only adverse events that are deemed related AND serious.

3.2 How will adverse event data be collected/recorded?

_____ Paper AE forms/source documents

__X__ Spreadsheet: paper or electronic

3.3. How will AEs be classified/graded?

__X__ Serious/Not serious

3.4 What scale will the PI use when evaluating the relatedness of adverse events to the study participation?

__X__ The PI will determine the relationship of adverse events to the study using the following scale:

Related: AE is clearly related to the intervention.
Possibly related: AE may be related to the intervention.
Unrelated: AE is clearly not related to intervention.

3.5 When will recording/reporting of adverse events/unanticipated problems begin?

____ After subject signs consent.

__x___After subject begins study drug/ device placement/intervention /study-related procedure/specimen collection.

3.6 When will the recording/reporting of adverse events/unanticipated problems end?

__X__ End of study drug/device/intervention/participation

3.7 How will Adverse Events, Unanticipated Problems, Protocol Violations and Data Breaches be reported? Complete the table below to answer this question.

Type of Event	To whom will it be reported:	Time Frame for Reporting	How reported?
Any internal event resulting in death that is deemed DEFINITELY related to (caused by) study participation *An internal event is one that occurs in a subject enrolled in a UVa protocol*	IRB-HSR	Within 24 hours	IRB Online and phone call www.irb.virginia.edu/
Internal, Serious, Related or Unexpected adverse event	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the	IRB Online www.irb.virginia.edu/

		event. *Timeline includes submission of signed hardcopy of AE form.*	
Protocol Violations/Noncompliance *The IRB-HSR only requires that MAJOR violation be reported, unless otherwise required by your sponsor, if applicable.* OR Enrollment Exceptions *See definition- only allowed if there is a commercial sponsor or a DSMB that has granted the enrollment exception.*	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Violation, Noncompliance and Enrollment Exception Reporting Form *http://www.virginia.edu/vprgs/irb/hsr_forms.html* *Go to 3rd bullet from the bottom.*
Data Breach	The UVa Corporate Compliance and Privacy Office ITC: if breach involves electronic data Police if breach includes items that are stolen: Stolen on UVA Grounds OR Stolen off UVa Grounds- contact police department of jurisdiction of last known location of PHI	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the time the incident is identified. IMMEDIATELY.	UVa Corporate Compliance and Privacy Office- Phone 924-9741 **ITC:** Information Security Incident Reporting procedure, http://www.itc.virginia.edu/security/reporting.html UVa Police-Phone- (434) 924-7166

4. How will the endpoint data be collected/recorded. Check all that apply

__X__ Protocol specific case report forms

5. Data and Safety Oversight Responsibility

5.1. Who is responsible for overseeing safety data for this study?

__X__ No additional oversight body other than PI at UVa Skip question 5.2

5.2. What is the composition of the reviewing body and how is it affiliated with the sponsor?

_____ Information may be found in the UVa Cancer Center Institutional DSMP

_____ Collaborative Site Analysis Study- see CSAS section of this DSMP

__X__ Other- N/A. No planned DSMB/DSMC per 5.1

5.3. What items will be included in the aggregate review conducted by the PI?

__X__ All adverse events

__X__ Unanticipated Problems

__X__ Protocol violations/Issues of noncompliance

_____ Audit results

_____ Application of dose finding escalation/de-escalation rules

_____ Application of study designed stopping/decision rules

__X__ Early withdrawals

__X__ Whether the study accrual pattern warrants continuation/action

__X__ Endpoint data

5.4 **How often will aggregate review occur?**

__X__ Annually

5.5. How often will a report, regarding the outcome of the review by the DSMB/DSMC, be sent to the UVa PI? N/A

5.6. How will a report of the information discussed in question 5.4 OR 5.5 be submitted to the IRB?

__X__ Part of IRB-HSR continuation status form

Payment

INSTRUCTIONS:

What is the difference between compensation and reimbursement?

A reimbursement is used when the subject is paid back for travel expenses such as mileage, lodging, food while traveling. Receipts or mileage must be submitted for a reimbursement.

Compensation is "payment" for things such as time, discomfort, inconvenience.

Total possible compensation should reflect the true value of the total possible dollar amount per participant for one year involvement in the study whether it be cash, check, gift card, goods, etc. or a combination of these items.

Retention "Gifts"- gifts may be given to a subject periodically during the study to remind them they are in the study. Sponsors may provide such items as water bottles, birthday cards etc. to the subject. NOTE: Cash or gift cards are NOT allowed as retention items.

1. **Are subjects being reimbursed for travel expenses** (receipts /mileage required)**?**

- If subject will NOT submit receipts for actual expenses (e.g. hotel, food, actual mileage) you MUST answer this NO.
- Reimbursements must be paid with Oracle Expenditure types found under the Travel Heading.
- For instructions on how to process a reimbursement please see "Goods and Services Procurement Guide" at http://www.procurement.virginia.edu/main/. You may also call the Procurement Help Desk at 924-4212.
- The money will not be reportable to the IRS as income, but will be withheld if the subject owes money to the state.

Yes.

►**IF YES, explain rate/ amount/ upper limits of reimbursements.**

Subjects will be reimbursed for cost of chest x-ray (standard of clinical care) if the hospital does not routinely cover and payment would constitute an undue burden to the enrollee. In addition, subjects will be reimbursed travel costs for visits after discharge from the hospital. As receipts are not available from means of local transportation at the sites, subjects will be reimbursed according to local standards based on distance travelled, with a maximum reimbursement of $20 USD.

►**IF YES, Do you confirm you are aware of the following procedures to follow for reimbursements?**

INSTRUCTIONS

- Subject will submit receipts for actual expenses (e.g. hotel, food, actual mileage).
- Reimbursements must be paid with Oracle Expenditure types found under the Travel Heading.
- For instructions on how to process a reimbursement see "Goods and Services Procurement Guide" at http://www.procurement.virginia.edu/main/. You may also call the Procurement Help Desk at 924-4212. The money will not be reportable to the IRS as income, but will be withheld if the subject owes money to the state.
- Reimbursements may not be done with gift cards

Yes. As subjects are unable to submit receipts because they are not available from local transportation at the study sites in the resource-limited settings of this study, subjects will be reimbursed according to local standards based on distance travelled, with a maximum reimbursement of $20 USD.

2. **Are subjects compensated for being in this study?**No.

Risk/ Benefit Analysis

1. What are the potential benefits for the participant as well as benefits which may accrue to society in general, as a result of this study?

The benefits to society may include a new drug dosage and/or regimen schema for the severe forms of TB that reduce overall morbidity and mortality. Capacity development as a result of this study will benefit the onsite laboratories and hospitals caring for patients with TB. There may be no direct participant benefit to the subjects, however subjects will be followed after treatment completion and discharge from the enrollment site which can be an improvement on local standards of care thereby allowing a potentially more rapid triage of a patient with symptom recurrence to medical care. Furthermore, similar patients in the future stand to receive considerable benefit.

2. Do the anticipated benefits justify asking subjects to undertake the risks?

The anticipated benefits justify the risks given the overall minimal risk procedures performed. Specifically, a patient's follow-up and monitoring performed for research purposes may have direct clinical benefit to the patient. The minimal risk procedures of phlebotomy, respiratory specimen, urine and stool collection will not directly benefit the patient but similar patients in the future stand to receive considerable benefit if the study reveals a pathway toward a new TB treatment approach. The capacity development required for this study will allow further research of local importance at the study site which could be of additional societal benefit.

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APPENDIX: Non- UVa Personnel

1. Explain the duties of non-UVA personnel on this protocol.

Esto Mduma MPH- Mr. Mduma is Research Director at the Haydom Lutheran Hospital (HLH) in Tanzania and long-standing collaborator with Drs. Houpt and Thomas in Haydom. He will direct activities at HLH including management of the study team.

Conrad Muzura MD- Dr. Conrad Muzoora is PI of the MUST site. He is a faculty member in the Department of Internal Medicine at Mbarrara University Science and Technology (MUST) has worked with UVA/ Dr. Moore for 5 years on sepsis and meningitis projects. He will oversee all aspects of the project at the study site, including management of the study team.

Stellah Mpagama MD, PhD- Dr. Mpagama is PI of the Tanzania- Kibong'oto site. She has worked with UVA for the last 5 years on TB related projects at Kibong'oto National TB Hospital where she is Director of Research. She will oversee all aspects of the project at the study site, including management of study site team.

Blandina Mbaga MD, PhD- Dr. Mbaga is director of Kilimanjaro Clinical Research Institute and will oversee the laboratory component for the Tanzania sites.

Sayera Banu MD, PhD- Dr. Banu is PI of the Bangladesh site. She has worked with UVA previously on TB diagnostic projects and directs the Mycobacteriology Laboratory at icddr,b where she is a Senior Scientist. She will oversee all aspects of the project at the study site, including management of the study site team.

Oleg Ogarkov, PhD- Dr. Ogarkov is PI of the Siberia site. He has worked with UVA and Drs. Heysell and Houpt for the last 3 years. He directs the microbiology laboratory and the Scientific Centre of the Family Health and Human Reproduction Problems, Irkutsk, Russia and the laboratory department at the Irkutsk TB Referral Hospital (site of patient enrollment). He will oversee all aspects of the project at the study site, including management of the study site team.

Charles Peloquin, PharmD, PhD- Dr. Peloquin directs the Pharmacokinetics Laboratory at the University of Florida and is a world's expert in pharmacokinetic/dynamic analyses for anti-TB medications. He will perform pharmacokinetic measurement on all study plasma samples shipped to University of Florida as described, as well as participate in pharmacokinetic/dynamic analysis.

2. **Explain your plans for training and oversight of these personnel**.

   All non-UVA personnel will be trained onsite by the UVA study team in execution of the protocol during onsite visits during the first 6 months of the project, monthly video conferencing thereafter, and an annual international meeting of all site PIs together.

3. **How do you plan to access any study records the non-UVA personnel might maintain?**

   Study records may be accessed during routine onsite visit by the PI or UVA co-investigators.

4. **Will the non- UVA personnel be exposed to any additional risk while working on this protocol?**
   No.

5. **List name of any other institution with which they have an affiliation**.

   Haydom Lutheran Hospital (HLH), Haydom Tanzania.

   Kilimanjaro Clinical Research Institute and Kibong'oto National TB Hospital, Kibong'oto Tanzania.

   Mbarara University Science and Technology (MUST) and Mbarara National Referral Hospital, Mbarara, Uganda.

   International Centre for Diarrheal Diseases Research, Bangladesh (ICDDR,B), and National Institute of Diseases of the Chest Hospital, Dhaka.

   Scientific Centre of the Family Health and Human Reproduction Problems and Irkutsk Tuberculosis Referral Hospital, Irkutsk, Russia

   University of Florida, Gainesville, Florida.

** All respective sites: Tanzania/ Haydom, Tanzania/ Kibong'oto, Bangladesh, Uganda, and Siberia, will obtain IRB approval.

6. Will the non- UVa personnel have access to UVa patients or their health information along with an y HIPAA identifiers prior to consent? No.

APPENDIX: International Research

1. Will this study be done outside the U.S. under the oversight of a UVA PI? Yes.

2. Provide the name and contact information for your onsite advisor.

Esto Mduma MPH- Research Director, Haydom Lutheran Hospital (HLH), Haydom, Tanzania. estomduma@gmail.com

Conrad Muzura MD- Department of Internal Medicine at Mbarrara University Science and Technology (MUST), Mbarara, Uganda. conradmuzoora@yahoo.com

Stellah Mpagama MD, PhD- Kibong'oto National TB Hospital and Kilimanjaro Clinical Research Institute, Moshi, Tanzania. sempagama@yahoo.com

Sayera Banu MD, PhD- ICDDR,B, Dhaka, Bangladesh. sbanu@icddrb.org

Oleg Ogarkov, PhD- Scientific Centre of the Family Health and Human Reproduction Problems, and Irkutsk Regional TB Referral Hospital. 3, K. Marx St. Irkutsk, Russian Federation. obogarkov@gmail.com

3. Provide the name and contact information for the local ethics committee or IRB.

Lubov Rychkova
Chair, Ethics Committee of the Scientific Centre of the Family Health and Human Reproduction
Irkutsk, Siberia, Russia
FWA 0002732

Dr Julius J. Massaga
Chair, Medical Research Coordinating Committee
National Institute for Medical Research
P.O. Box 9653
Dar es Salaam, Tanzania

Dr. Abbas Bhuiya
Chair, Research Review Committee
International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b)
GPO Box 128
Dhaka 1000, Bangladesh
FWA-00001468

Dr. Peter Ndemere

Executive Secretary, Uganda National Council for Science and Technology
Plot 6, Kimera Road, Ntinda
P.O.Box 6884
Kampala, Uganda
FWA00001293

4. Are either of the following statements true?

- **UVa personnel will travel abroad to conduct this study**
- **You plan to send supplies abroad for this study**

Yes.

5. Who are the "stakeholders" in the region you are visiting (e.g. local health provider, community leader, local colleague, etc.)?

Primarily the local colleagues listed above as site PIs as they are leaders in TB research in their local region.

6. Do you confirm you have discussed this project with them and that they are in support of this study?
Yes.

7. Do you confirm that the PI of this protocol has experience in this field of research and also has experience in the country in which you plan to do your research?
Yes.

8. Are there risks to research subjects, particularly those due to power imbalances (e.g. between subject and researcher; between subject and individuals/groups receiving research results?
No.

9. Are there risks to subjects due to language differences and cultural sensitivities? No.

10. Are there any additional local requirements for permissions, licenses or agreements beyond local IRB approval? No.

11. Will any of the data gathered internationally be brought back to UVa? NO

IF YES, will any of the following HIPAA identifiers be included with the information?

☐ Yes ☒ No	1. Name
☐ Yes ☒ No	2. All geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of the zip code if, according to the current publicly available data from the Bureau of the Census: (1) The geographic unit formed by combining all zip codes with the same 3 initial digits contains more than 20,000 people and (2) The initial 3 digits of a zip code for all such geographic units containing 20,000 is changed to 000.
☐ Yes ☒ No	3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may

	be aggregated into a single category of age 90 or older. *[This means you may record the year but not record the month or day of any date related to the subject if the subject is under the age of 89. In addition if the subject is over the age of 89 you may not record their age and you may not record the month, day or year of any date related to the subject]*
☐Yes ☒ No	4. Telephone numbers
☐Yes ☒ No	5. Fax numbers
☐Yes ☒ No	6. Electronic mail addresses
☐Yes ☒ No	7. Social Security number
☐Yes ☒ No	8. Medical Record number
☐Yes ☒ No	9. Health plan beneficiary numbers
☐Yes ☒ No	10. Account numbers
☐Yes ☒ No	11. Certificate/license numbers
☐Yes ☒ No	12. Vehicle identifiers and serial numbers, including license plate numbers
☐Yes ☒ No	13. Device identifiers and serial numbers
☐Yes ☒ No	14. Web Universal Resource Locators (URLs)
☐Yes ☒ No	15. Internet Protocol (IP) address numbers
☐Yes ☒ No	16. Biometric identifiers, including finger and voice prints
☐Yes ☒ No	17. Full face photographic images and any comparable images
☐Yes ☒ No	18. Any other unique identifying number, characteristic, code that is derived from or related to information about the individual (e.g. initials, last 4 digits of Social Security #, mother's maiden name, first 3 letters of last name.)
☐Yes ☒ No	19. Any other information that could be used alone or in combination with other information to identify an individual. (*e.g. rare disease, study team or company has access to the health information and a HIPAA identifier or the key to the code* .)

APPENDIX: Legal/Regulatory

Recruitment

The following procedures will be followed:

- Finders fees will not be paid to an individual as they are not allowed by UVa Policy.
- All recruitment materials will be approved by the IRB-HSR prior to use. They will be submitted to the IRB after the IRB-HSR has assigned an IRB-HSR # to the protocol.
- Only those individuals listed as personnel on this protocol will recruit and or conduct the consenting process with potential subjects.

Retention Incentives

Any item used by the sponsor/ study team to provide incentive to a subject to remain in the study, other than compensation identified in the Payment section, will be submitted to the IRB for review prior to use. The IRB-HSR will provide the study team with a Receipt Acknowledgement for their records. Retention incentive items are such things as water bottles, small tote bags, birthday cards etc. Cash and gift cards are not allowed as retention incentives.

Clinical Privileges

The following procedures will be followed:

- Investigators who are members of the clinical staff at the University of Virginia Medical Center must have the appropriate credentials and been granted clinical privileges to perform specific clinical procedures whether those procedures are experimental or standard.
- The IRB cannot grant clinical privileges.
- Performing procedures which are outside the scope of the clinical privileges that have been granted may result in denial of insurance coverage should claims of negligence or malpractice arise.
- Personnel on this protocol will have the appropriate credentials and clinical privileges in place before performing any procedures required by this protocol.
- Contact the Clinical Staff Office- 924-9055 or 924-8778 for further information.

Sharing of Data/Specimens

Data and specimens collected under an IRB approved protocol are the property of the University of Virginia. You must have "permission" to share data/ specimens outside of UVa other than for a grant application and or publication. This "permission" may come in the form of a contract with the sponsor or a material transfer agreement (MTA) with others. A contract/ MTA is needed to share the data outside of UVa even if the data includes no HIPAA identifiers and no code that could link the data back to a HIPAA identifier.

- No data will be shared outside of UVa, beyond using data for a grant application and or publication, without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.
- No specimens will be shared outside of UVa without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.

Prisoners

If the original protocol/ IRB application stated that no prisoners would be enrolled in this study and subsequently a subject becomes a prisoner, the study team must notify the IRB immediately. The study team and IRB will need to determine if the subject will remain in the study. If the subject will remain in the study, the protocol will have to be re-reviewed with the input of a prisoner advocate. The prisoner advocate will also have to be involved in the review of future continuations, modifications or any other reporting such as protocol violations or adverse events.

Prisoner- Individuals are prisoners if they are in any kind of penal institution, such as a prison, jail, or juvenile offender facility, and their ability to leave the institution is restricted. Prisoners may be convicted felons, or may be untried persons who are detained pending judicial action, for example, arraignment or

trial. For additional information see the OHRP website at: http://www.hhs.gov/ohrp/policy/populations/index.html

Compensation in Case of Injury

If a subject requests compensation for an injury, the study team should notify the IRB-HSR (924-9634/2439847) the UVa Health System Patient Relations Department (924-8315). As a proactive courtesy, the study team may also notify UVa Health System Patient Safety and Risk Management (924-5595).

On request, the study team should provide the Risk Management Office with the following information/documents:

- Subject Name and Medical Record Number
- Research medical records
- Research consent form
- Adverse event report to IRB
- Any letter from IRB to OHRP

Subject Complaints

During a research study, the study team may receive complaints from a subject. If the study team is uncertain how to respond to a complaint, or is unable to resolve it with the subject, the study team may contact the IRB-HSR (924-9634/243-9847), the UVa Health System Patient Relations Department (924-8315).

Request for Research Records from Search Warrant or Subpoena

If the study team receives a request for research records from a search warrant or subpoena, they should notify UVa Health Information Services at 924-5136. It is important to notify them if information from the study is protected by a Certificate of Confidentiality.

APPENDIX: Recruitment

1. How do you plan to identify potential subjects?—Subjects will not be enrolled at UVA

a. ____ Chart Review/ Clinic Schedule Review/ Database Review from a database established for health care operations (departmental clinical database) or an Improvement Project (*e.g. Performance Improvement, Practice Improvement, Quality Improvement*).

b. _____ Review of a database that was established to keep data to be used for future research such as the CDR, departmental research database or use of data from a separate current active research protocol.

c. _____ Patients UVa health care provider supplies the UVa study team with the patients contact information without patients' knowledge.

d. _____ Patient obtains information about the study from their health care provider. The patient contacts the study team if interested in participating. (Health care provider may or may not also be the a member of the study team)

e. _____ Potential subjects will not be directly identified. They will respond to an advertisement such as a flyer, brochure etc.

f. _____ Potential subjects have previously signed a consent to have their name in a registry/database to be contacted for future studies of this type.

g. _____ Other*:* Specify

If item # a, b or c is checked above and if this protocol involves the use of protected health information do you confirm the following to be true?

- The use or disclosure is sought solely to review protected health information as necessary to prepare the research protocol or other similar preparatory purposes.
- No PHI will be removed from the UVa covered entity.
- The PHI that the researcher seeks to use or access is necessary for the research purposes.

Yes.

2. How will potential subjects be <u>contacted? UVA subjects not enrolled in study</u>

a. ____ Direct contact of potential subjects by the study team via letter, phone, direct e-mail. Members of study team ARE NOT health care providers of patients. Information will not be collected from psychotherapy notes.

b. ___ Potential subjects will be approached while at the study hospital by a person who is NOT a member of their health care team. Information will not be collected from psychotherapy notes.

c. ____ Direct contact of potential subjects by the study team by approaching in person at UVa or via letter, phone, direct e-mail. Members of study team contacting potential subjects ARE health care providers of patients.

d. ____ Indirect contact (flyer, brochure, TV, broadcast emails, patient provided info about the study from their health care provider and either the patient contacts study team or gives their healthcare provider permission for the study team to contact them.)

e. ____ Potential subjects are not patients. The study does not include obtaining subjects health information. Subjects will be contacted directly via email, phone, letter or presentation in group setting with consent then obtained individually in a private setting.

3. **Will any additional information be obtained from a potential subject during "prescreening"?** No.

Do you confirm that health information with HIPAA identifiers will not be shared outside of UVa until a consent form is signed or only shared in a de-identified manner? Yes.

4. **Do you plan to ask the subjects to do anything, other than answering questions, for the study prior to signing a consent?** No.

5. How will the consenting process take place with either the prospective subject, the subject's legally authorized representative or parent/legal guardian of a minor (if applicable)?

The study will be discussed with the potential subject or parent/guardian in a private area of the patient care setting in the hospital in the patient's own language. After each section of the consent the potential subject or parent/guardian will be asked to review the section and verbally confirm understanding. All questions will be answered prior to obtaining written consent. Children ages 7-15 will also provide assent. Study procedures of chart review and baseline specimen collection will begin immediately after enrollment.

6. Will subjects sign a consent form for any part of the study? Yes.

7. Will the study procedures be started the same day the subject is recruited for the study?

No, but if the potential subject or parent/guardian signs consent on the day of recruitment, then study procedures of chart review and baseline specimen collection will begin immediately after enrollment. Otherwise the potential subject or parent guardian will be given 24 hours to make a decision to consent. Waiting longer may risk subjects being initiated on TB treatment for longer periods of time prior to specimen collection.

8. Is there the potential to recruit economically or educationally disadvantaged subjects, or other vulnerable subjects such as students or employees? Yes

There are economically and educationally disadvantaged people among the patient population. Subjects will be asked questions to ensure all participants, especially those who are more vulnerable, understand their participation is completely voluntary.

9. Do you need to perform a "dry run" of any procedure outlined in this protocol? No.

APPENDIX: Participation of Children

1. Explain why this research topic is relevant to children.

Of the ~9 million people diagnosed with TB each year, ~1 million will be children. Pediatric TB is understudied and children at the proposed study sites suffer a considerable morbidity and mortality that may improved with completion of this study.

2. Is the knowledge being sought in this study already available for children or is it currently being acquired through another ongoing study? No.

3. Provide data that is available in adults in order that the IRB may judge the potential risk in children. If there is no adult data available, provide reasons why not. If this information is available in a sponsor's protocol, you may reference the section # here and not duplicate the information.

Low drug AUCs were predictive of treatment outcomes for drug-susceptible pulmonary TB in adults from South Africa [26]. Children in this study will be treated for drug-susceptible pulmonary TB and we will also more rigorously exclude non-TB related diseases (often treated as TB in resource-limited settings), and when a

cultured *M. tuberculosis* isolate is obtained, we will obtain the more refined pharmacodynamics index of AUC/MIC, which to date has not been studied in the pediatric population.

4. **Is the potential subject population likely to include wards of the state or children who are more at risk for becoming a ward of the state?** No.

   4a. Is the research is this protocol related to the childs' status as a ward of the state? No.

   4b. Is the research to be conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards? No.

   4c. Are you aware of the following requirement?

   If the consent form contains a signature line for both parents the study team will notify the IRB immediately, if at any time during the course of the research, it becomes known that a potential subject is a ward of the state or that a child already enrolled in this protocol becomes a ward of the state.

   Yes.

5. **Does this study involve a placebo arm** No.

6. **Will UVa researchers conduct the study outside the state of Virginia?**Yes.

   ►**IF YES, explain any applicable state law from the state in which the research is being conducted that might affect the consenting process.**

   At the international study sites mentioned, children are defined as <15 years of age. Potential subjects 15 years or greater are treated on the adult wards of the hospitals.

APPENDIX: Privacy Plan for Studies with Consent/HIPAA Authorization

1. Answer the questions below to describe the plan to protect the data from improper use and disclosure.

1A. Will any HIPAA identifiers be <u>collected</u> or <u>received</u> by the UVa study team ? NO

YES	NO	HIPAA Identifier
	x	1. Name
	x	2. Postal address information, other than town or city, state, and zip code
	x	3. Age if over the age of 89 OR Date of Birth if over the age of 89
	x	4. Telephone numbers
	x	5. Fax numbers
	x	6. Electronic mail addresses
	x	7. Social Security number
	x	8. Medical Record number
	x	9. Health plan beneficiary numbers
	x	10. Account numbers
	x	11. Certificate/license numbers
	x	12. Vehicle identifiers and serial numbers, including license plate numbers
	x	13. Device identifiers and serial numbers
	x	14. Web Universal Resource Locators (URLs)
	x	15. Internet Protocol (IP) address numbers
	x	16. Biometric identifiers, including finger and voice prints
	x	17. Full face photographic images and any comparable images
	x	18. Any other unique identifying number, characteristic, code that is derived from or related to information about the individual (e.g. initials, last 4 digits of Social Security #, mother's maiden name, first 3 letters of last name.)
	x	19. Any other information that could be used alone or in combination with other information to identify an individual. *e.g. rare disease or the study data /specimen is kept with a code and the study team also has the KEY to the code. Check this item even if the key to the code will only be kept temporarily while data is being collected.*

1E. The following procedures must also be followed.

- Only investigators for this study and clinicians caring for the patient will have access to the data. They will each use a unique login ID and password that will keep confidential. The password should meet or exceed the standards described on the Information Technology Services (ITS) webpage about *The Importance of Choosing Strong Passwords.*
- Each investigator will sign the University's Electronic Access Agreement forward the signed agreement to the appropriate department as instructed on the form.
- UVa University Data Protection Standards will be followed: http://www.virginia.edu/informationsecurity/dataprotection.
- If identifiable data is transferred to any other location such as a desktop, laptop, memory stick, CD etc. the researcher must follow the University's "Electronic Storage of Highly Sensitive Data Policy". Additional requirements may be found in the Universities Requirements for Securing Electronic Devices.
- If identifiable health information is taken away from the UVa Health System, Medical Center Policy # 0218 will be followed.
- The data will be securely removed from the server/drive, additional computer(s), and electronic media according to the University's Electronic Data Removal Policy.

- The data will be encrypted or removed if the electronic device is sent outside of UVa for repair according to the University's Electronic Data Removal Policy.
- If PHI will be faxed, researchers will follow the Health System Policy # 0194.
- If PHI will be emailed, researchers will follow the Health System Policy # 0193 and University Data Protection Standards .
- The data may not be analyzed for any other study without additional IRB approval.
- If you are using patient information you must follow Health System Policy # 0021.
- Both data on paper and stored electronically will follow the University's Record Management policy and the Commonwealth statute regarding the Destruction of Public Records.

Summary of Requirements to Comply with UVa Health System, Medical Center and University Policies and Guidance as noted above:

Highly Sensitive Data is:
-personal information that can lead to identity theft if exposed or
-health information that reveals an individual's health condition and/or history of health services use.
Protected Health Information (PHI) a type of Highly Sensitive Data, is health information combined with a HIPAA identifier
Identifiable Health Information under HIPAA regulations is considered to be *Highly Sensitive Data at UVa.*
A **Limited Data Set** (LDS) under HIPAA regulations is considered to be *Moderately Sensitive Data at UVa. The only HIPAA identifiers associated with data: dates and or postal address information limited to town or city, state, and zip code.* See Table A below for details.

Highly Sensitive Data (Identifiable Health Info per HIPAA)	**Moderately Sensitive Data (Limited Data Set and De-identified data per HIPAA)**
General Issues	*General Issues*
Discussions in private Do not share with those not on the study team or those who do not have a need to know.	Do not share with those not on the study team or those who do not have a need to know
Password protect	Password protect
Physically secure (lock) hard copies at all times if not directly supervised. If not supervised hard copies must have double protection (e.g. lock on room OR cabinet AND in building requiring swipe card for entrance).	Physically secure (lock) hard copies at all times if not directly supervised.
For electronic documents turn off File Sharing; turn on firewalls; use up to date antivirus and antispyware; delete data securely.	For electronic documents turn off File Sharing; turn on firewalls; use up to date antivirus and antispyware; delete data securely.
Encrypt See Encryption Solutions Guidance *Files on Health System Network drives are automatically encrypted. If not stored there it is study teams responsibility to make sure data are encrypted.*	
If device sent out for service or repair, encrypt or remove data AND contract for repair using a UVa Purchase order.	If device sent out for service or repair, encrypt or remove data AND contract for repair using a UVa Purchase order.
Store files on a network drive specifically designated for storing this type of data, e.g. high-level security server/drives managed by Information Technology Services or the “F” and “O” managed by Heath Systems Computing Services. You may access it via a shortcut icon on your desktop, but you are not allowed to take it off line to a local drive such as the desktop of your computer (e.g. C drive) or to an individual Use Device*. May access via VPN	
Do not share with sponsor or other outside group before consent is obtained or the IRB has granted appropriate approvals and contract/ MTA is in place	Do not share with sponsor or other outside group before consent is obtained or the IRB has granted appropriate approvals and contract/ MTA is in place
If collected without consent/ HIPAA authorization will NOT be allowed to leave UVa HIPAA covered entity unless disclosure is approved by the IRB and the disclosure is tracked in EPIC	If collected without consent/ HIPAA authorization will NOT be allowed to leave UVa HIPAA covered entity unless disclosure is approved by the IRB and an MTA is in place prior to sharing of data

Highly Sensitive Data (Identifiable Health Info per HIPAA)	**Moderately Sensitive Data (Limited Data Set and De-identified data per HIPAA)**
Electronic Data Collection & Sharing	*Electronic Data Collection & Sharing*
(e.g. smart phone app, electronic consent using tablet etc.) MUST consult with ISPRO or Health System Web Development Office: 434-243-6702 University Side: IT-Security@virginia.edu Health System: Web Development Center:	
Individual-Use Device	*Individual-Use Device*
Do not save to individual-use device* without written approval of your Department AND VP or Dean. If approval obtained, data must be password protected and encrypted.	
Do not save an email attachment containing HSD to an individual use device (e.g. smart phone)	
E Mail	*E Mail*
Do not share via email with Outlook Web/ or forward email using other email vendors like Gmail/ Yahoo	
Do not send via email on smart phone unless phone is set up by Health System	
Email may include name, medical record number or Social Security number only if sending email to or from a person with * HS in their email address. *NOTE: VPR & IRB staff do not meet this criteria!*	In addition to sharing LDS, may include initials if persons sending and receiving email work within the UVa HIPAA covered entity.**
FAX	*FAX*
Verify FAX number before faxing	Verify FAX number before faxing
Use Fax Cover Sheet with Confidentiality Statement	Use Fax Cover Sheet with Confidentiality Statement
Verify receiving fax machine is in a restricted access area	Verify receiving fax machine is in a restricted access area
Verify intended recipient is clearly indicated	Verify intended recipient is clearly indicated
Recipient is alerted to the pending transmission and is available to pick it up	Recipient is alerted to the pending transmission and is available to pick it up immediately

Highly Sensitive Data (Identifiable Health Info per HIPAA)	**Moderately Sensitive Data (Limited Data Set and De-identified data per HIPAA)**
Electronic Data Collection & Sharing	*Electronic Data Collection & Sharing*
(e.g. smart phone app, electronic consent using tablet etc.) MUST consult with ISPRO or Health System Web Development Office: 434-243-6702 University Side: IT-Security@virginia.edu Health System: Web Development Center: Contract must include required security measures.	
May NOT be stored in places like UVaBox, UVaCollab, QuestionPro. May also NOT be stored in non-UVa licensed cloud providers, such as Dropbox, Google Drive, SkyDrive, Survey Monkey, etc.	May be stored in places like UVaBox, UVaCollab, QuestionPro. May NOT be stored in non-UVa licensed cloud providers, such as Dropbox, Google Drive, SkyDrive, Survey Monkey, etc.
LOST OR STOLEN:	*LOST OR STOLEN:*
Must report in accordance with protocol/ in accordance with the Information Security Incident Reporting Policy. Any data breach will also be reported to the IRB of Record if the report meets the criteria of an Unanticipated Problem.	Must report in accordance with protocol/ in accordance with the Information Security Incident Reporting Policy. Any data breach will also be reported to the IRB of Record if the report meets the criteria of an Unanticipated Problem.

** Individual Use Device – examples include desktop computer, smart phone app, flash (thumb) drive, tablet, laptop, CD, C drive of your computer)*

***The UVa HIPAA covered entity is composed of the UVa VP Office of Research, the Health System, School of Medicine, School of Nursing, Nutrition Services (Morrison's), the Sheila C. Johnson Center, the Exercise and Sports Injury Laboratory and the Exercise Physiology Laboratory.*