Strategic approach to implementing modified STR for MDR-TB (DESTRoy TB initiative)

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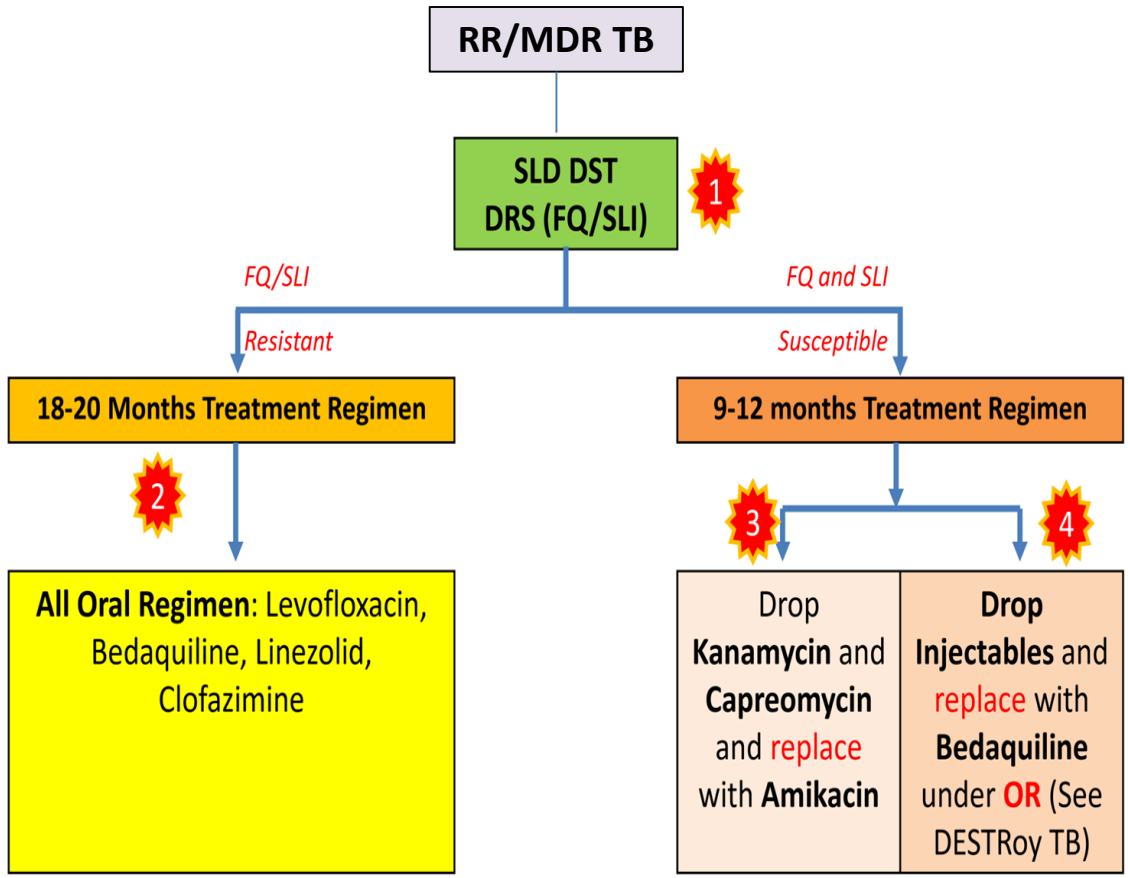
RR/MDR TB Treatment Options



Evaluation of a Modified STR

DESTRoy TB:

D*iscovering* ***E****vidences* ***S****upporting the effectiveness of new* ***T****reatment for drug* ***R****esistant Tuberculosis*

Open-label single-arm study to assess the country-specific **feasibility** and to measure the **effectiveness** of a new treatment regimen of 40 weeks (9 months) duration in patients with pulmonary rifampicin resistant (RR) and multi drug resistant (MDR) tuberculosis

Primary Objectives

Effectiveness

- Interim treatment outcomes (at 4th and 6th months)
- End of treatment outcome (Relapse rate at 6 and 12 months after the end of treatment)

Operational feasibility

- Proportion of enrolled patients on the study regimen (MDR-TB / RR-TB patients of the total MDR-TB/RR-TB patients detected and enrolled on drug resistant TB treatment)
- Adherence of the treatment facilities to the study protocol procedures
- Acceptability by the managers (national and regional), treatment centers, satellite treatment centers and patients (qualitative analysis)

Secondary objectives

- To evaluate the safety and tolerability (frequency and severity of adverse drug reactions (ADRs)) of a treatment regimen of 40 weeks (9 months) duration consisting of Bdq-Lzd-Lfx-Cfz in patients with Fluoroquinolone Susceptible RR/MDR TB
- To evaluate the safety and tolerability (frequency and severity of adverse drug reactions (ADRs)) of a treatment regimen of 40 weeks (9 months) duration consisting of Bdq-Dlm-Lfx-Cfz in patients with Fluoroquinolone Resistant RR/MDR TB
- To determine the time to sputum culture conversion with this combination treatment regimen
- To measure loss to follow up

Study outcomes

Primary Outcome Measures

- Favorable efficacy outcome (Cure and Treatment Completed outcomes as defined by the national policy) at the end of treatment with the study regimen

Secondary Outcome Measures

- Incidence of bacteriological relapse during 60 weeks (12 months) post-treatment follow-up, after a favorable response (Cure and Treatment Completed outcomes as defined by the national policy)
- Incidence of bacteriologic failure or clinical failure during treatment period of 40 weeks (9-months)
- Treatment Adverse Events (TAEs) presented by incidence of:

- Grade 3 or higher adverse events of any type at any time while on combination treatment regimen (safety)
- Discontinuation of study drug(s) for any reason (tolerability)
- All-cause mortality during treatment or follow-up

- Time to sputum culture conversion from positive to negative in the Liquid (MGIT) or LJ culture system (defined as the interval between the date of treatment initiation and the date of acquisition of the first of two consecutive negative cultures taken at least 4 weeks apart)

Inclusion Criteria

All patients with diagnosed MDR-TB or rifampicin resistance will be invited to participate in the 40 weeks all-oral short treatment protocol if they:

- Have pulmonary TB (smear-positive or smear-negative); Chest X-Ray results consistent with pulmonary TB (taken as part of the initial clinical assessment)
- No previous use of second-line drugs for one month or more
- Men or women aged 12 years and above (Are at least 15 (18) years of age at the time of enrolment)
- Are willing to attend a treatment facility for the intensive phase of the 40-weeks regimen, and the treatment facility or a local treatment site for the continuation phase and follow-up period
- Have signed an informed consent, including acceptance of full treatment duration of 9 months and follow-up duration of 12 months after the end of treatment
- HIV status - HIV infected and uninfected patients are allowed in the study

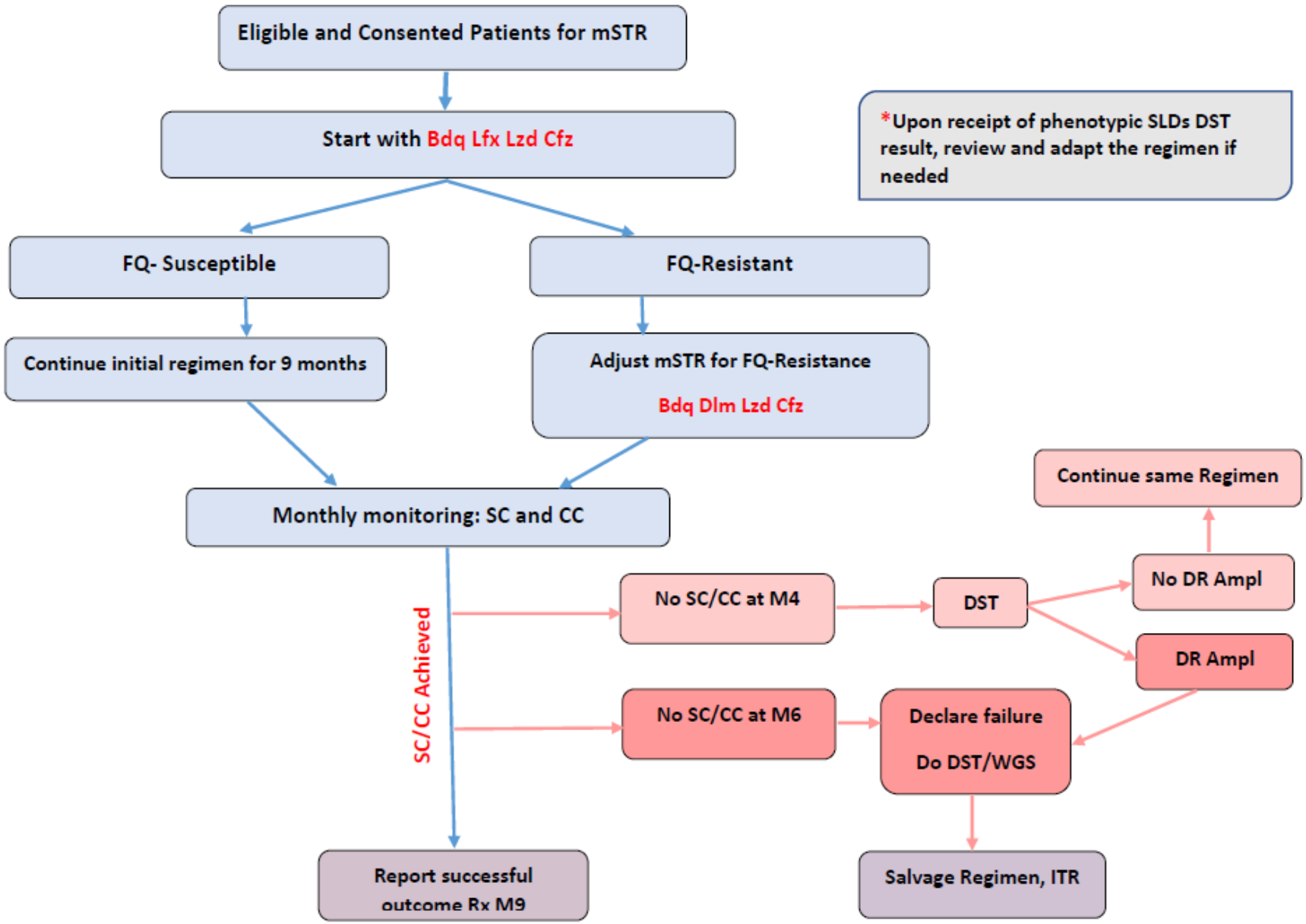
  Patients already on antiretroviral treatment (ART) will be allowed in the study. The antiretroviral treatment regimen will be evaluated for any contraindications to the drugs used
  HIV infected patients at any CD4 count irrespective of antiretroviral treatment commencement and duration will be included in the study

Exclusion Criteria

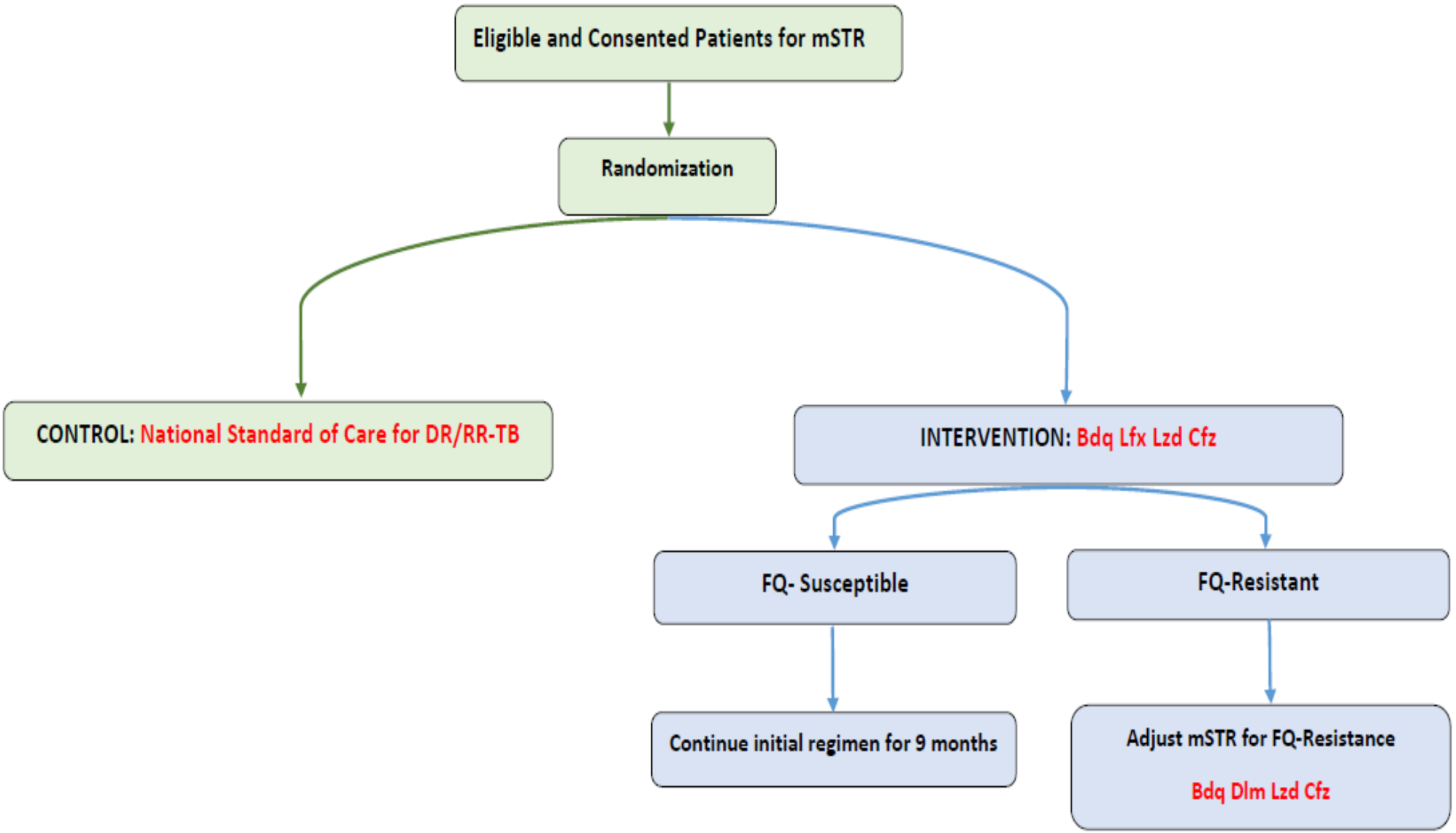
Patients with any of the following criteria will not be eligible for the 40-weeks all-oral short treatment protocol:

- Have a heart rate-corrected QT (QTc) interval of ≥450msec on ECG at screening
- Have AST or ALT > 3 times the upper limit of normal
- Have a creatinine clearance below 20 mL/min per 1.73 m^2 body surface area
- Have severe or intractable extra-pulmonary TB, such as tuberculous meningitis or miliary tuberculosis
- Have extra-pulmonary TB, unless pulmonary TB is also present
- History of allergy or known hypersensitivity to any of the trial Investigational Medicinal Products or related substances
- Are taking any medications contraindicated with the medications in the study treatment regimen
- Have any condition (social or medical) which in the opinion of the investigator would make study participation unsafe
- Are unwilling or unable to sign an informed consent
- Are pregnant or breastfeeding
- Are unable to attend or comply with treatment or the follow-up schedule

Proposed DESTRoy Treatment Algorithm



Randomized Design



		TREATMENT									FOLLOW-UP					
Clinical evaluation	Screening	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12	Month 15	Month 18	Month 21
Sputum smear	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sputum culture	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest X-ray	X						X									X
Written informed consent	X															
Demographics, Medical History	X															
Clinical Examination	X	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical assessment (including AEs and concomitant medication during treatment)		X*	X	X	X	X	X	X	X	X						
Hemoglobin/platelets count	X			X			X			X						
White blood count	X			X			X			X						
Serum creatinine	X			X			X			X						
Serum potassium	X		X		X		X		X							
Thyroid stimulating hormone	X															
Serum liver enzymes	X	X	X	X	X	X	X	X	X	X						
ECG	X	X**	X	X	X	X	X	X	X	X						
Pregnancy test (female)	X															
HIV test	X															

*****Patients will be examined at least once a week for the first month of treatment and thereafter monthly throughout treatment.*

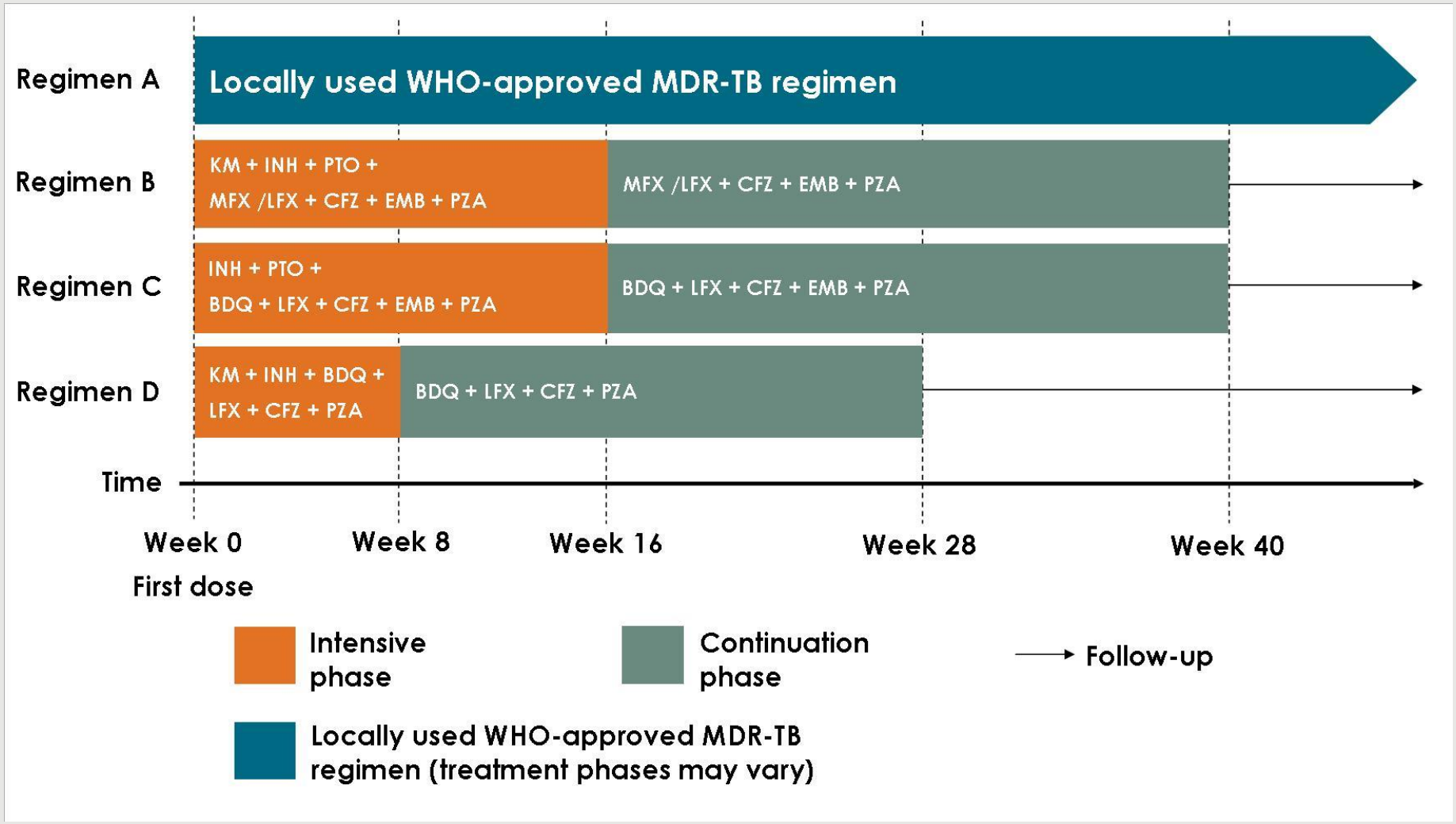
*******Baseline ECG should be obtained and additional ECGs conducted at week 1 and 2 after starting treatment and thereafter monthly throughout treatment. ECG should be repeated as necessary in case of clinical suspicion of heart rhythm and conduction disturbances.*

Cost Exercise (Philippines)

	Drug Cost for 1 DRTB pt	Rx Monitoring Cost	Patient Support Cost
SSTR: **4 AMK MFX PTO CFZ H E Z / 5 MFX CFX E Z**	**$710**	$ 424	$ 540
SLTR FQ-S: **6 BDQ, 18 LZD, 18 LFX, 18 CFZ**	**$1,730**	$ 774	$ 1,080
SLTR FQ-R: **6 BDQ, 6 DLM, 18 LZD, 18 CFZ, 18 CS**	**$3,853**	$ 774	$ 1,080
mSTR FQ-S: **9 BDQ, 9 LFX, 9 LZD, 9 CFZ**	**$1,225**	$ 443	$ 540
mSTR FQ-R: **9 BDQ, 9 DLM, 9 LZD, 9 CFZ**	**$3,998**	$ 443	$ 540

STREAM II

Treatment phases of investigational regimens



Following implementation of protocol Version 8.0 recruitment to Regimen A and D has been discontinued and in Regimen B moxifloxacin has been replaced by levofloxacin

STREAM II: Updates

- Recruitment to Regimen A is being halted in light of the ongoing rollout of the shorter treatment regimen as the standard of care in national TB programs. Recruitment to Regimen D also is being halted because of the decreased public health relevance of an MDR-TB regimen that contains injectables

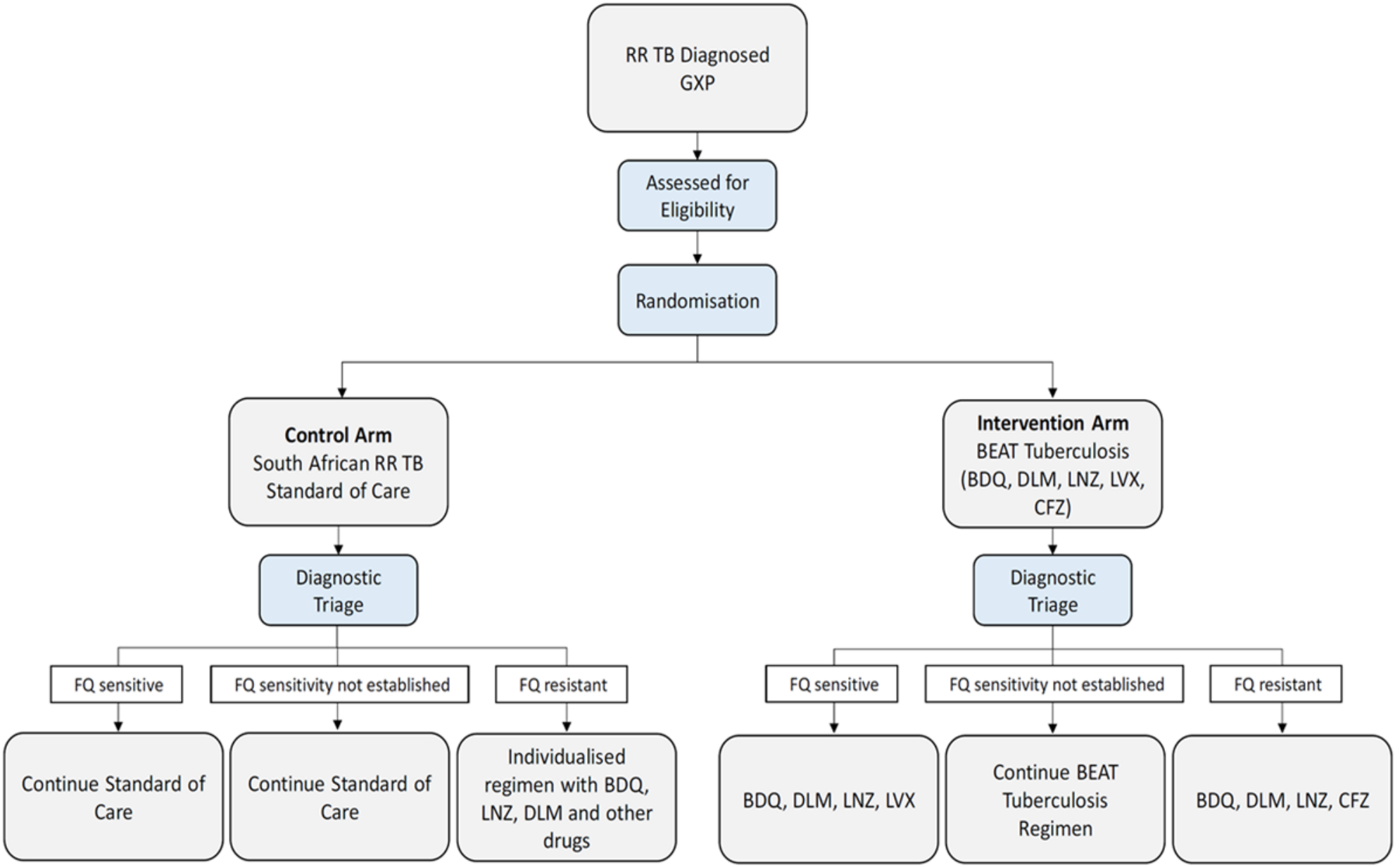
- Enrolment began in April 2016 in Mongolia, and currently a total of 13 sites in Georgia, Moldova, Mongolia, Ethiopia (two sites), South Africa (four sites), Uganda, and India (three sites) are participating in the trial. **421 participants** had been enrolled in Stage 2 of the trial

- South Africa: recruitment has been stopped in Q3 2018 in response to the change in the standard of care to an all oral bedaquiline regimen, the four South African sites had recruited a total of 92 participants, accounting for almost 25% of total recruitment. The trial teams continue to provide care to all participants already recruited

- Recruitment for Stage 2 is expected to be completed by late 2019

- Initial Stage 2 results are expected to be available in 2021

BEAT Tuberculosis (Building Evidence for Advancing new Treatment for Tuberculosis), SA



Study Sites

Implementing partners:
WHC Clinical HIV Research Unit (CHRU) study team

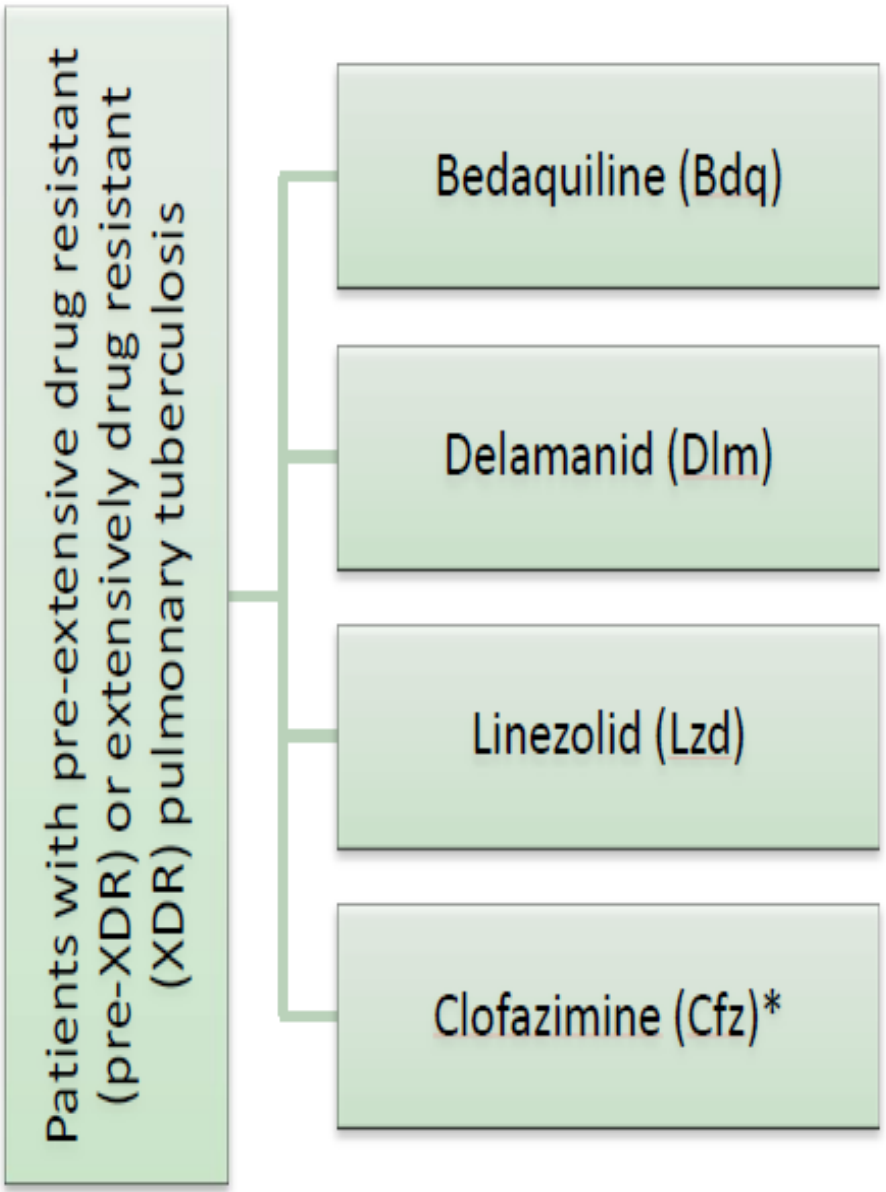
Site 1:
Empilweni TB Hospital, Port Elizabeth, Eastern Cape

- Enrollment has been planned to start in July 2019

Site 2:
The Jose Pearson TB Hospital, Port Elizabeth, Eastern Cape

- Enrollment has been planned to start in November 2019

BEAT TB, India



Drug	Body weight			
	16-29 Kg	30-45 Kg	46-70Kg	>70Kg
Clofazimine	100mg	100mg	200mg	200mg
Linezolid	300mg	600mg	600mg	600mg
Bedaquiline	400 mg OD for 2weeks, 200mg TIW for 22weeks			
Delamanid	100mg BD for 24-36 weeks			

24 WEEKS OF TREATMENT

Additional 12 weeks if sputum culture positive at 16 weeks

FOLLOW-UP FOR 72-84 WEEKS *from the enrollment*

Study Sites

- *National Institute for Research in Tuberculosis (NIRT), Chennai*
- *B.J. Medical College (BJMC), Ahmedabad, Gujarat India*
- National Institute of Tuberculosis and Respiratory Diseases (Autonomous Institute under the Ministry of Health & Family Welfare Govt. of India), New Delhi
- *Rajan Babu Institute of Pulmonary Medicine & Tuberculosis (RBIPMT), New Delhi*
- The Group of TB Hospital (GTB), Sewri, Mumbai

Challenges

Use of BDQ/DLM combination (not enough data)

Requirements for ALL study medications DST (Lnz, Cfz – routing DST in India, DLM – Otsuka provided methodology/pure powder, BDQ -- *The WHO Technical Manual for Drug Susceptibility Testing of Medicines Used in the Treatment of Tuberculosis (http://apps.who.int/iris/handle/10665/275469): recommends MGIT as the preferred drug susceptibility testing method for Bedaquiline and a critical concentration of 1 mg/ml; Availability of Bedaquiline pure powder -- the NIH AIDS Reagent Program (https://www.aidsreagent.org/register.cfm) the drug is free-of-charge but the requester might have to pay for shipping*)

Study design – requesting a randomized trial (India)

High cost of DLM (under negotiation)

Concern with Lzd and duration

Bedaquiline and repurposed drugs for fluoroquinolone-resistant MDR-TB: how much better are they? Bastard M, et. al., July 2018, AJRCCM,

A total of 140 patients with pulmonary TB were included, 91 in the non-CU cohort and 49 in the CU-cohort. The two cohorts presented similar characteristics at treatment initiation (Table), although in the CU cohort more patients had been previously treated for MDR-TB ($p<0.001$), had had previous treatment with clofazimine ($p<0.001$), and had XDR-TB ($p=0.058$). All patients in the CU cohort received bedaquiline and linezolid, 76.0% received imipenem/cilastatin plus amoxicillin/clavulanate, and 83.7% received clofazimine as part of the treatment regimen. In the CU cohort, clofazimine use was more frequent ($p<0.001$) and the total number of drugs received at initiation was higher ($p <0001$).

Faster culture conversion in CU (2.7 mth vs 5.7 mth, p=<0.001)
Higher culture conversion rate at 6 mth (73.0 % vs 35.2%, p=<0.001)
TSR was higher in CU (61.2% vs 22.0%, p=<0.001)

Vigilance in AEs monitoring is important!

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Principles for constructing a tuberculosis treatment regimen: the role and definition of core and companion drugs

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Table Activity of anti-tuberculosis drugs and their use

	Characteristics*			Use in a MDR/XDR–TB treatment regimen			
	Bactericidal activity	Sterilizing activity	Resistance prevention	Core drug†	Companion drug used for its high bactericidal effect‡	Companion drug used for its sterilizing effect	Other companion drugs
RMP§	High	High	High				
FQ (GFX/MFX$^{high\text{-}dose}$)¶	High	High	High	X			
BDQ	High	High	High	X			
DLM	High	High?	High	?	X		
Second-line injectables#	High	Low	High		X		
LZD	High	Low	High		X		
Imipenem/meropenem + amoxicillin-clavulanate	High	?	High		X		
CFZ**	Low	High	High			X	
PZA††	Low	High	Low			X	
ETH/PTH‡‡	Moderate/high	Low	Moderate				X
INH$^{high\text{-}dose}$	Low/moderate§§	Low	High				X
EMB	Low	Low	Moderate				X
CS	Moderate	Low?	Moderate				X
PAS	Low	Low	Moderate				?

AGORA
RESEARCH LETTER

Compassionate use of delamanid in combination with bedaquiline for the treatment of multidrug-resistant tuberculosis

Cite this article as: Hafkin J, Hittel N, Martin A, *et al*. Compassionate use of delamanid in combination with bedaquiline for the treatment of multidrug-resistant tuberculosis. *Eur Respir J* 2019; 53: 1801154 [https://doi.org/10.1183/13993003.01154-2018].

199 CU Request

164 started Rx with Dlm

84 Bdq & Dlm Combo (73.8% XDR, 21.4 PreXDR)

58 completed 24 wks

58 completed 24 wks

CC 87.9%

No CC 6.9%

Ukn/Pending 5.2%

Other companion drugs: Lzd, Cfz, Z, FQ, PAS

QTc prolongation, 5 pts (6%), but only 1 >500 ms, resolved a/f stopping Cfz

CC Without Bdq (n=65):
80% CC (n=65), 16.9% No CC, 3.1% unk/pending