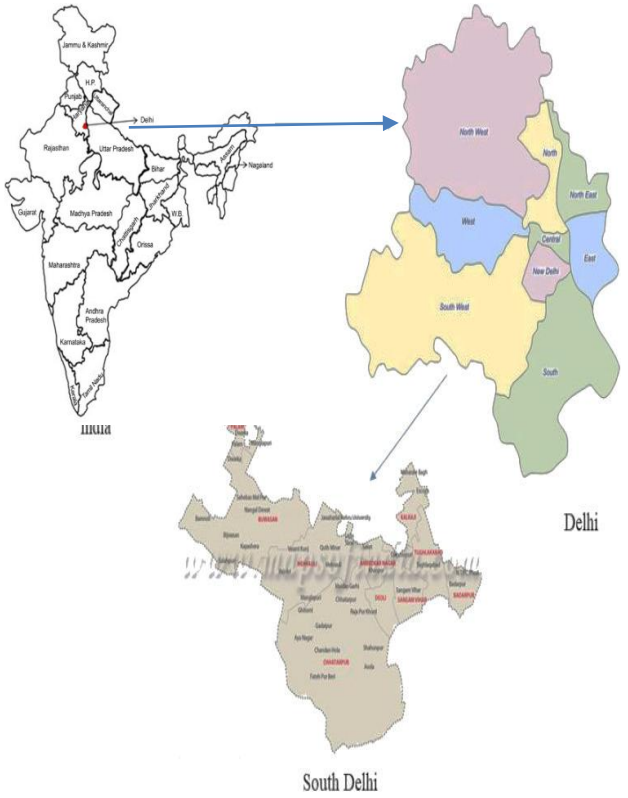
Pediatric Newer Drugs Study (PND Study)

DR. SANGEETA SHARMA
MD, MNAMS, FNCCP(I)
Consultant & In charge,
National Centre of Excellence for Pediatric TB
Former Director,
National Institute of Tuberculosis and Respiratory Diseases,
New Delhi

DETAILS OF THE RESEARCH PROJECT



Pediatric Newer Drugs Study: PND Study

Safety and Tolerability of Bedaquiline and Delamanid along with Optimized Background regimen for treatment of Paediatric DRTB (RR/ MDR/ Pre-XDR/XDR TB) in children aged 6-18 Years

- **Trial No.:** CTRI/2022/05/042659
- **Design**: Open Label, 3 arm, Single center, Randomized controlled adaptive trial.
- **Funded:** Indian Council of Medical Research (ICMR), New Delhi
- **Trial site:** National Centre of Excellence for Pediatric TB and DRTB,
- National Institute of Tuberculosis and Respiratory Diseases, New Delhi.
- **Sample Size**: 219 (73 subjects/arm)
- **Status**: Ongoing

Ministry of Health & Family Welfare
Government of India

Methods

Study primary endpoints:

• Interim outcome (culture conversion, clinico-radiological)

•Final outcome (cure, treatment completed, treatment failure, LTFU, death)

Study secondary endpoints:

• **S**afety (number of AE, SAE ≥ 3) and Tolerability

Ethics:

• Ethical Committee, NITRD, New Delhi

Study Funded by

• Indian Council of Medical Research (ICMR), New Delhi.

Study Supported by

• Central TB Division, Ministry of Health & Family Welfare, Govt. of India

Study Monitored by

• External Drug Safety Monitoring Board (DSMB)

Ministry of Health & Family Welfare Government of India

Objectives

Primary Objective

- To evaluate the **safety** and **tolerability** of newer drugs, BDQ and DLM.
- To **compare the efficacy** of **Shorter (6-9 month) combined BDQ + DLM** alongwith Optimized Background regimen (OBR) *with* **Longer (18-20 month) regimen of BDQ / DLM alongwith OBR** in paediatric (6-18 Year old) confirmed or probable DR TB patients (RR/ MDR/ Pre XDR/ XDR).

Secondary Objective

- To compare **treatment outcomes (interim and final)** of 3 Arms.
- To evaluate **adherence** and **palatability of child friendly drug formulations (CFD).**
- To **compare the relapse rate** at the end of 6^{th} and 12^{th} month post treatment follow-up period for all cohorts (preferably also in subjects who prematurely discontinue from study trial).
- Evaluate development of resistance to drugs used in the regimens.
- Feasibility of adopting these All oral injection free regimens for pediatric DRTB patients under programmatic conditions.

Eligibility Criteria

- Confirmed (RR/ MDR/ Pre XDR/ XDR TB), Probable DRTB
- 6-18 years
- PTB &/- EPTB all sites including CNS TB, Miliary TB, OA
- Non Severe/ Severe disease
- HIV +/-
- Comorbidities +/-
- Consenting Guardian
- Place of residence Delhi/NCR

Study Design

Probable or Confirmed MDR/ RR/ Pre XDR/ XDR Diagnosis

Informed Consent

Pre Treatment Evaluation

Randomization 1:1:1

Longer BDQ Regimen

Longer DLM Regimen

Shorter BDQ + DLM Regimen

Allocation of Arm & start of Regimen*

Hospital admission (1st 2-4wks) Not mandatory)
- Stabilization
- DOT
- Clinical monitoring
- Therapeutic education & counseling

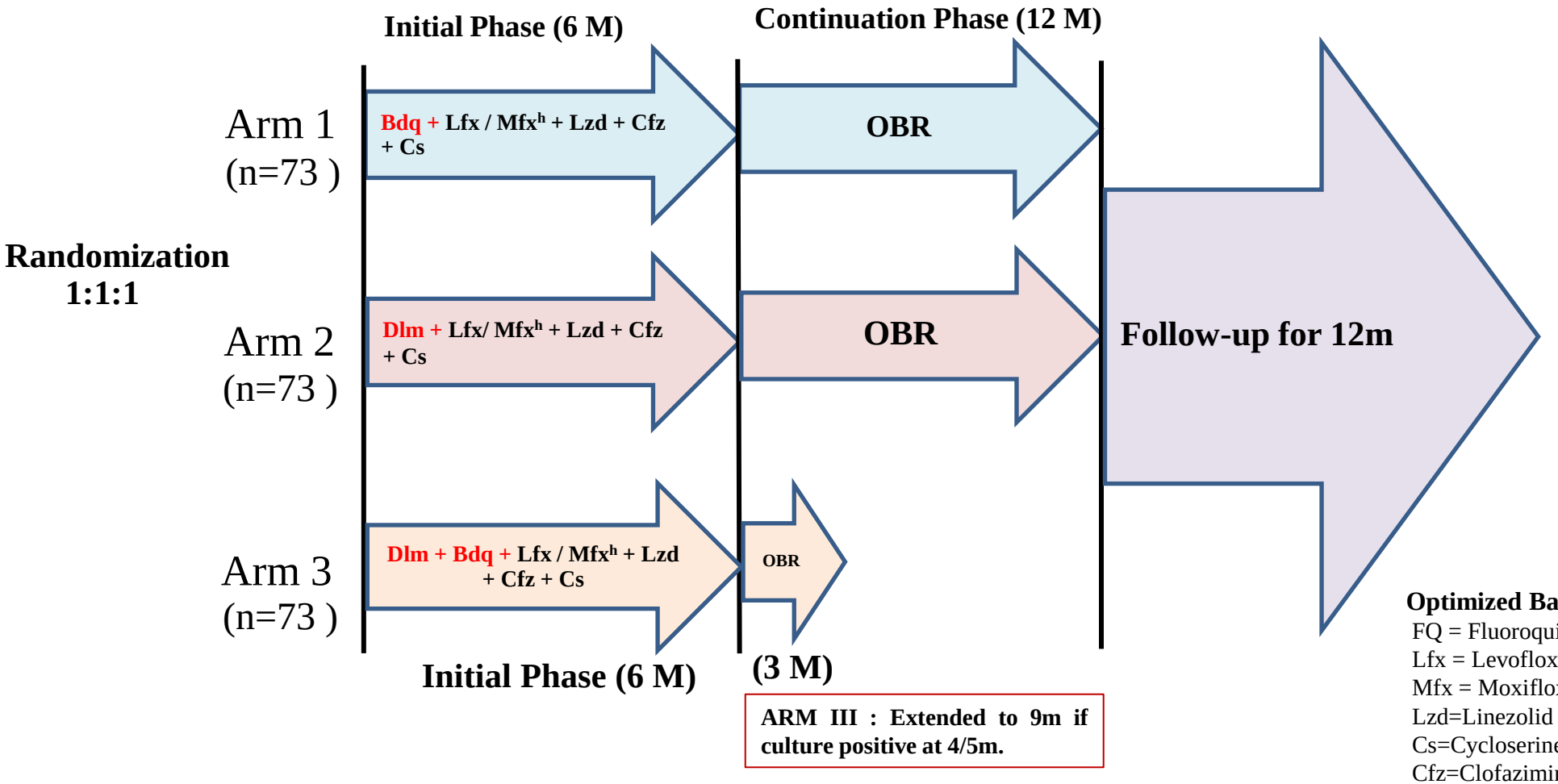
Eligibility of F-DOT (SAT) → Patient/guardian Choice

30 day Drug Supply + EXTRA

Weekly Phone Call SAT sessions → Clinical Condition; Assess adherence, challenges; Treatment Tolerance & acceptability

Monthly Follow-up Clinic visits:
- Clinical monitoring, check Adherence, Tolerance & acceptability
- Smear & Culture every month x 1st 6 Month & then Quarterly till End of treatment.
- Blood parameters (as per protocol)
- X Ray done at beginning, at the end of 6 month & as and when required.

Treatment Regimens

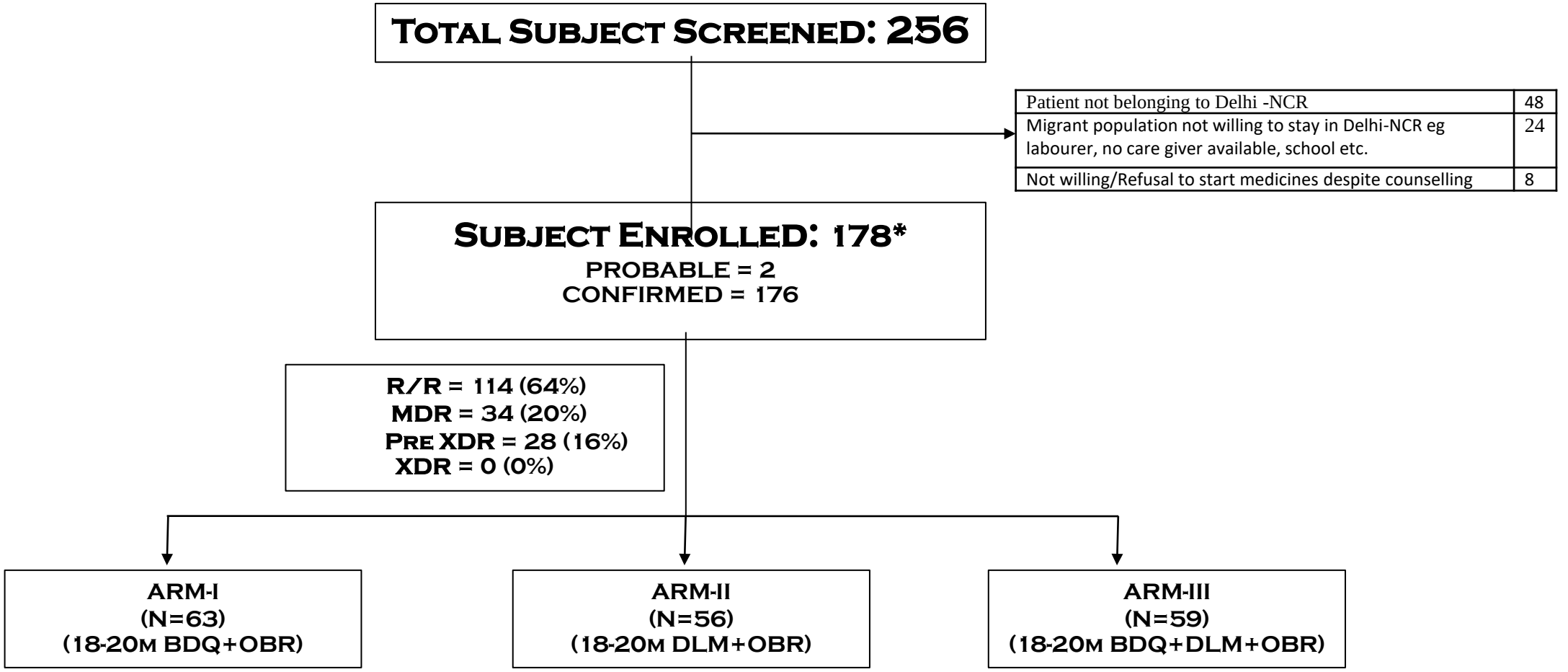


Optimized Background Regimen (OBR) :
FQ = Fluoroquinolone (LFX/ MFX)
Lfx = Levofloxacin
Mfx = Moxifloxacin
Lzd=Linezolid
Cs=Cycloserine
Cfz=Clofazimine
+/- Group C drugs
(added in sequence Amikacin, PZA Ethionamide, PAS, Ethambutol, Meropenem)

Drug dosages given mg/kg weight band WHO recommendation 2022 (Module – 5)

Design Adaptation: Group C drugs added based on DST/ intolerance/ failure of regimen

Results


Total Subject Screened: 256
Patient not belonging to Delhi -NCR 48
Migrant population not willing to stay in Delhi-NCR eg labourer, no care giver available, school etc. 24
Not willing/Refusal to start medicines despite counselling 8
Subject Enrolled: 178*
PROBABLE = 2
CONFIRMED = 176
R/R = 114 (64%)
MDR = 34 (20%)
Pre XDR = 28 (16%)
XDR = 0 (0%)
ARM-I
(N=63)
(18-20M BDQ+OBR)
ARM-II
(N=56)
(18-20M DLM+OBR)
ARM-III
(N=59)
(18-20M BDQ+DLM+OBR)

Study Participants Enrolled (till date) N:178

Mean age 14.8years

Characteristics at baseline (N=178)	Category	Arm-I (N=63)	Arm-II (N=55)	Arm-III (N=58)	Total	p-Value
Age (Years)	6-10 years	8	16	6	30 (17%)	<0.005(significant)
	11-18 years	55	40	53	148 (83%)	
Sex	Male	24	18	22	64 (36%)	<0.005(significant)
	Female	39	38	37	114 (64%)	
Contact (with TB patients)	Present	15	20	16	51 (28.7%)	<0.005(significant)
	Absent	48	35	44	127 (71.3%)	
HIV	Positive	0	0	0	0	- <0.005(significant)
	Negative	63	56	59	178 (100%)	
DIABETES (RBS)	Present	0	0	0	0	- <0.005(significant)
	Absent	63	56	59	178 (100%)	
Nutrition	Underweight (<2 Sd)	31	32	32	95 (53.3%)	<0.005(significant)
	Normal	28	20	19	67 (37.6%)	
	Overweight (>2 Sd)	5	4	7	16 (9%)	
Monthly Income	Low Income	45	45	42	132 (74%)	<0.005(significant)
	Medium Income	15	10	14	39 (22%)	
	High Income	4	1	2	7 (4%)	

Disease Profile
N:178

At baseline (N=178)	Category	Arm-I (N=63)	Arm-II (N=56)	Arm-III (N=59)	Total	p-Value
TB Location						
PTB		**48**	**32**	**45**	**125 (70%)**	<0.005 (Significant)
PTB Only		39	22	39	100 (56%)	
PTB with EPTB*		9	10	6	25 (14%)	
	LN	4	7	2		
	GI	6	3	3		
	Pl. Eff	4	1	2		
	Bone-jt	1	-	-		
	CNS	1	-	-		
EPTB*		**15**	**24**	**14**	**53 (30%)**	
	LN	11	17	8		
	GI	5	3	0		
	Pl. Eff	3	3	8		
	Bone-jt	5	3	1		
	CNS	0	1	0		
Dise1se Profile on Radiology						
	U/L Non Extensive	17	7	16	**40**	
	B/L Non Extensive	2	0	2	**4**	
	U/L Extensive	8	14	14	**36**	<0.005 (Significant)
	B/L Extensive	21	11	13	**45**	

***(>1 site involved)**

Microbiological Characteristics
N= 178

At baseline (N=176)	Category	Arm-I	Arm-II	Arm-III	Total N (%)	p-Value
Smear microscopy	Positive	23	16	20	59 (33)	
	Negative	36	38	37	111 (63)	<0.005 (Significant)
	Not Done	4	2	2	8 (4)	
NAAT	Positive	61	56	57	174 (98)	<0.005 (Significant)
	Negative	2	0	2	4 (2)	
	Invalid/indeterminate	0	0	0	0 (0)	
	Not Done	0	0	0	0 (0)	
Culture	Positive	34	29	35	98 (55)	<0.005 (Significant)
	Negative	23	20	17	60 (34)	
	Contaminated/Not done	4	3	2	9 (5)	
	Awaited	2	4	5	11 (6)	
DST	RR	48	40	26	114 (64)	<0.005 (Significant)
	MDR	8	12	14	34 (19)	
	Pre XDR	6	3	19	28(16)	
	XDR	0	0	0	0(0)	
	Probable MDR	1	1	0	2 (1)	

Fluoroquinolone Resistance

Regimens	FQ - S	FQ –R*	FQ -NK	Total (N)
	N	N	N	
Arm I	56	6	1	63
Arm	52	3	1	56
Arm III	40	19	0	59
Total (N)	148	28	2	178

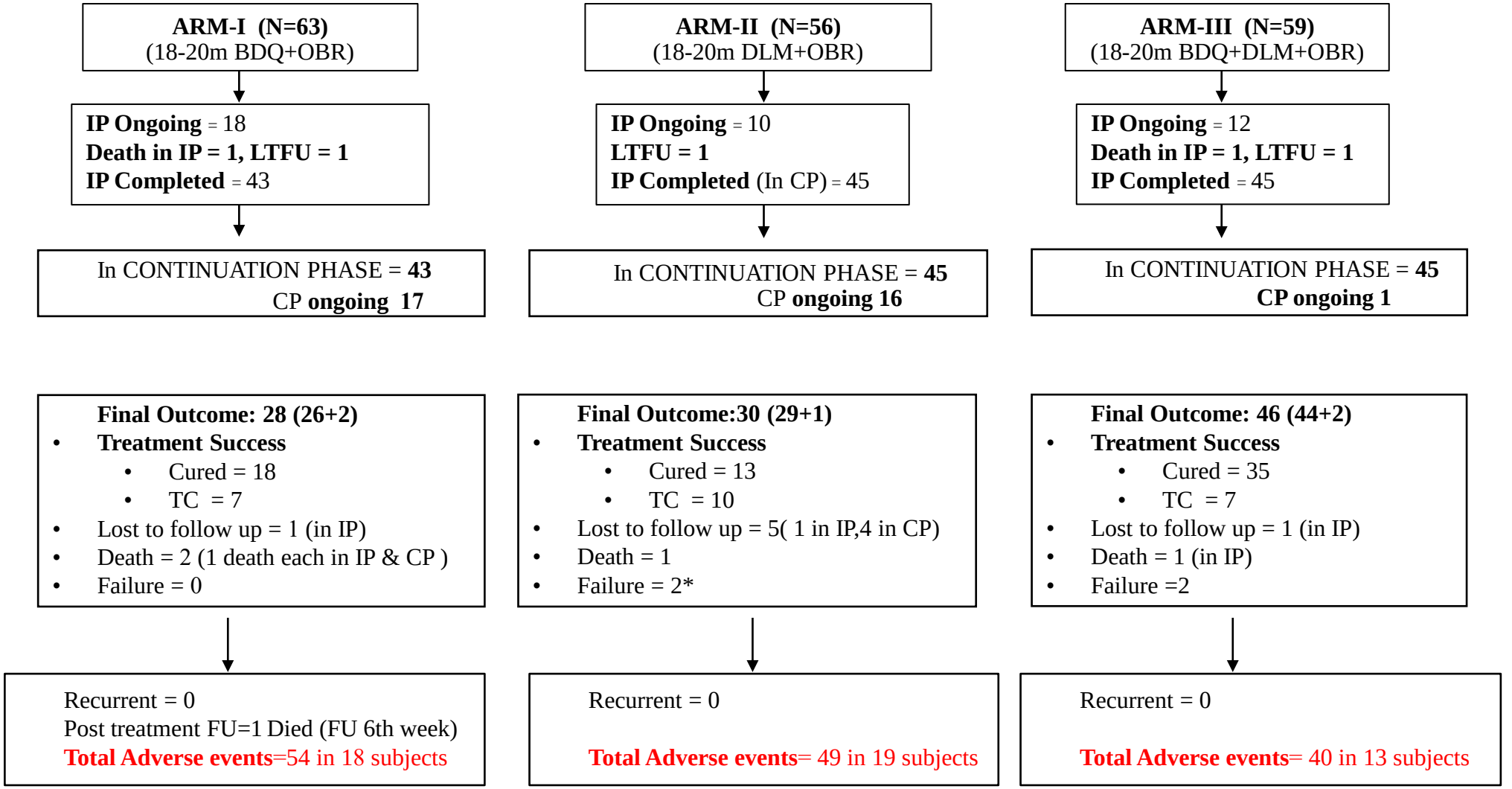
P-value is < 0.005 (Significant)

INTERPRETATION : The number of FQ sensitive subjects is significantly more than FQ resistant subjects

- Result received retrospectively Regimen adaptation: Group C drugs added based on DST/ intolerance/ failure of regimen

RESULTS

N= 178 (100%) with SAT or f-DOT on discharge from hospital after initial stabilization



•Result received retrospectively Regimen adaptation: Group C drugs added based on DST/ intolerance/ failure of regimen

LTFU: Lost to follow up
TC: Treatment completed

*Both Patients shifted to Arm-III, 1 died at 2m of starting Arm-III, but not counted under Arm-III,

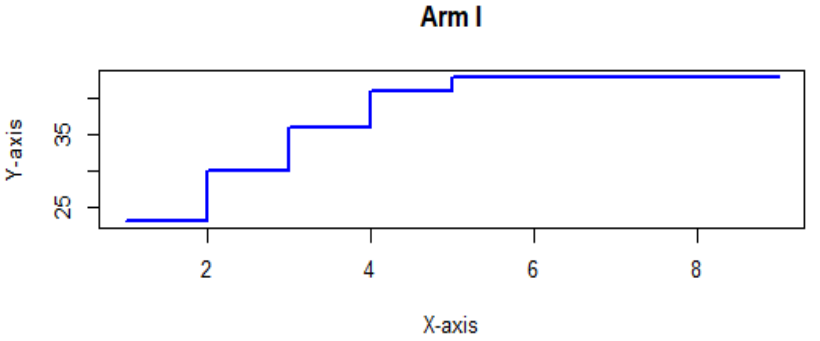
(Enrollment ongoing to reach target of 219)

Sputum Conversion Arm Specific (in months)

Interpretation: On comparison, conversion at months 4,5th , 8th, 9th Arm I has significantly faster conversion rate than Arm II and Arm III.

ARM I : 43

	1 M	2 M	3 M	4 M	5 M	6 M	7 M	8 M	9 M
ARM I	23	7	6	5	2	0	0	0	0

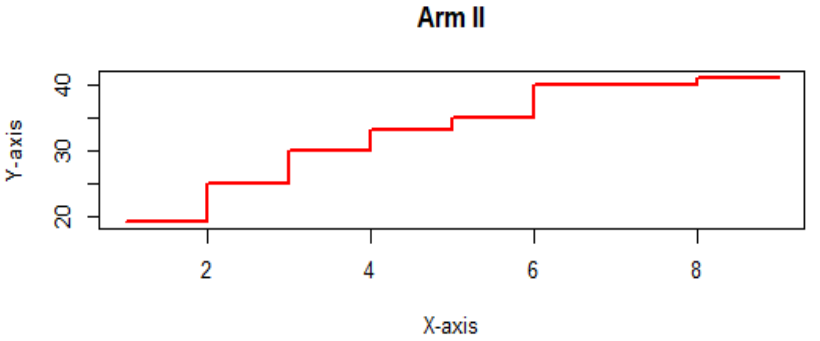


Conversion : 43/63

- **Treatment Success**
  - Cured = 18
  - TC = 7
- Lost to follow up = 1
- Death = 2 (1 death each in IP & CP)
- Failure = 0

ARM II : 41

	1 M	2 M	3 M	4 M	5 M	6 M	7 M	8 M	9 M
ARM II	19	6	5	3	2	5	0	1	0

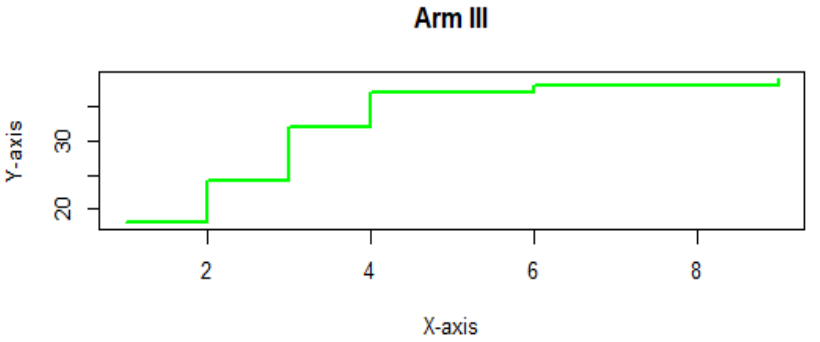


Conversion : 41/56

- **Treatment Success**
  - Cured = 13
  - TC = 10
- Lost to follow up = 5 (1 in IP)
- Death = 0
- Failure = 2*(Shifted to Other Arm (Failure at 8 month)

ARM III : 39

	1 M	2 M	3 M	4 M	5 M	6 M	7 M	8 M	9 M
ARM III	18	6	8	5	0	1	0	0	1

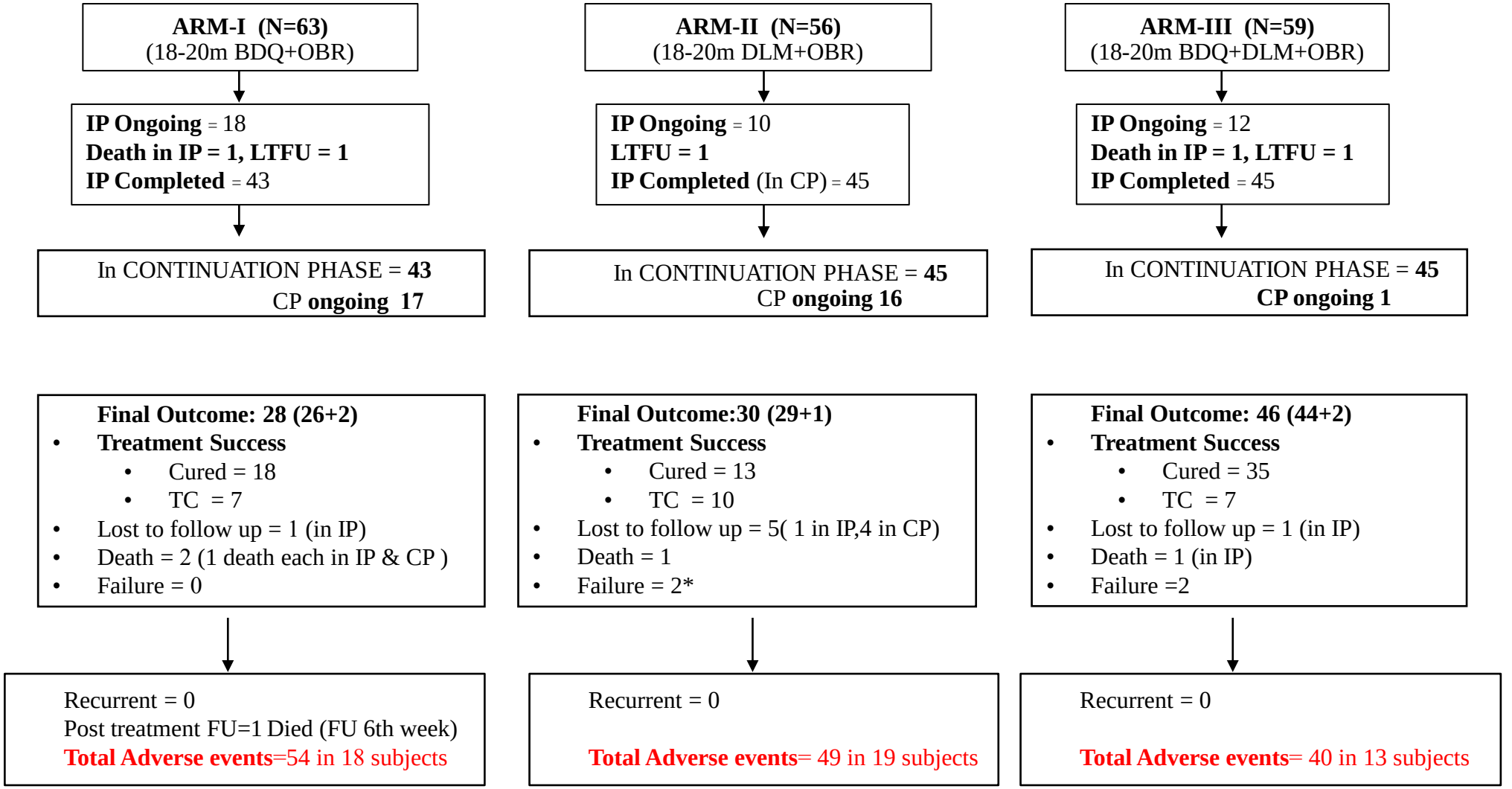


Conversion : 39/59

- **Treatment Success**
  - Cured = 35
  - TC = 7
- Lost to follow up = 1 (in IP)
- Death = 1 (in IP)
- Failure =2 *(Shifted to ITR at 8 month)

RESULTS

N= 178 (100%) with SAT or f-DOT on discharge from hospital after initial stabilization



•Result received retrospectively Regimen adaptation: Group C drugs added based on DST/ intolerance/ failure of regimen

LTFU: Lost to follow up
TC: Treatment completed

*Both Patients shifted to Arm-III, 1 died at 2m of starting Arm-III, but not counted under Arm-III,

(Enrollment ongoing to reach target of 219)

Treatment Delivery

- **N= 178 (100%) SAT or f-DOT on discharge from hospital after initial stabilization**
- **N= 74/178 (42%) Ongoing treatment**
- **N= 104/178 (58%) Completed treatment**
  - **N= 90/104 (87%) treatment success**
  - **N= 14/104 (13%) Unfavorable treatment outcomes**
  - **N=5/178 (2.8%) Death**
  - **N= 1/178 (0.5%) Interrupted treatment due to SAE ≥ 3**
  - **N= 7/178 (4%) lost to follow-up**

Arm II
Ran away from home (4 mo)
Changed address ; on Inj Am (10mo),
shifted to village; on Inj Am (2.5mo)
Not interested in taking medicines despite counselling.
Arm III
Ran away from orphanage (1 mo)

Outcome without LTFU

ARM I

LTFU=1

Final Outcome:28

- **Treatment Success**
  - Cured = 18
  - TC = 7
- Death = 2 (1each in IP & CP)
- Failure = 0

Success without LTFU
25/27 = 92%

ARM II

LTFU=5

Final Outcome:30

- **Treatment Success**
  - Cured = 13
  - TC = 10
- Death = 1
- Failure = 2*

Success without Defaulters
23/25 = 92%

ARM III

LTFU=1

Final Outcome:46

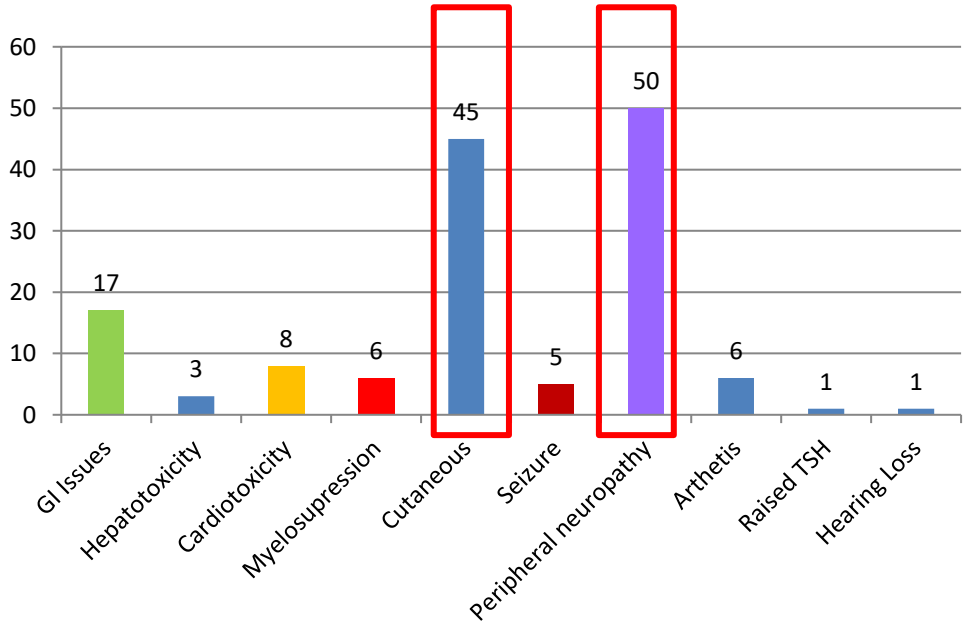
- **Treatment Success**
  - Cured = 35
  - TC = 7
- Death = 1 (in IP)
- Failure =2

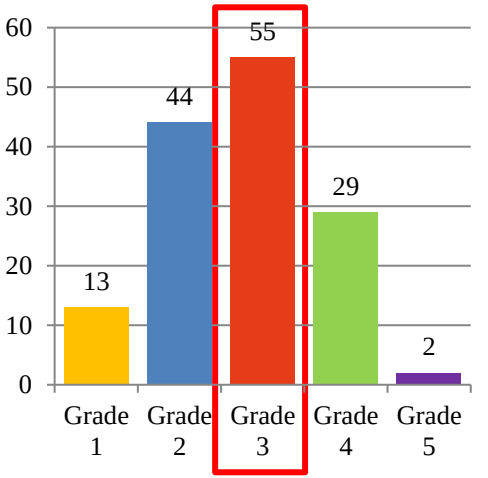
Success without Defaulters
42/45 = 93%

•N=5/178 (2.9 %) Death rate without LTFU

Adverse drug effects

		Arm I					Arm II					Arm III				
	SAE Grade	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
1	GI Issues	-	4	1	1	-	-	1	3	-	-	-	2	5	-	-
2	Hepatotoxicity	-	-	1	1	-	-	-	-	1	-	-	-	-	-	-
3	Cardiac issues	-	-	-	1	1	-	–	1	1		-	-	1	2	1
4	Hematological	-	-	1	1	-	-	-	1	1	-	-	1	1	-	-
5	Cutaneous	-	14	2	-	-	13	2	-	-	-	-	14	-	-	-
6	Seizure	-	-	-	3	-	-	-	-	2	-	-	-	-	-	-
7	Peripheral neuropathy	0	3	10	5	-	-	2	14	3	-	-	-	8	5	-
8	Arthritis	-	1	2	-	-	-	-	3	-	-	-	-	-	-	-
9	Raised TSH	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-
10	Hearing Loss	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-





Detecting and assessing ADE side effects of drugs and prevention of these episodes

Repeated patient/care giver counseling sessions by project staff educating them regarding early recognition of common symptoms, early reporting of ADE has lead to a noticeable difference eg. any kind of leg pain , staff is informed telephonically and appropriate action initiated as per grade of ADE.

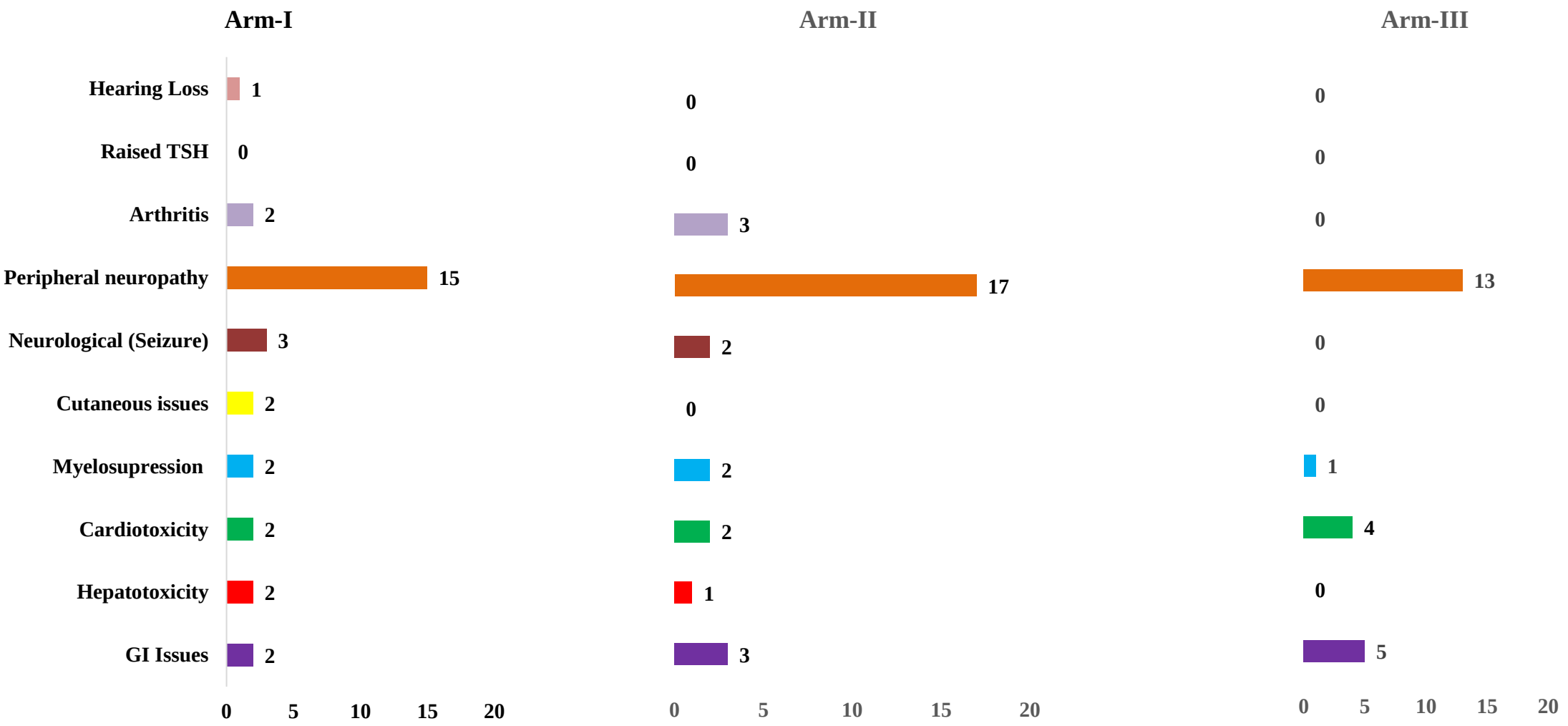
n= 143 episodes observed in 50 patients

N = 84 SAE observed; among 45 subjects

- Commonest Grade 1 &2 was Cutaneous followed by Gastritis.
- Commonest Grade 3 were Peripheral Neuropathy
- Myelosuppression requiring treatment interruption uncommon as all arms were started after building up Hb> 10gm% : occurred in 6 children only.
- Seizures Grade 4(4 GTCS, I focal) occurred in 05 children (Arm I = 3 & Arm II = 2) : stabilized on Levetriacetam. except 1 patient ArmI who died.
- * Others included body aches, fatigue, malaise, generalized weakness

SERIOUS ADVERSE EVENTS (GRADE ≥ 3)

N = 84 SAE observed; among 45 subjects



Acceptability

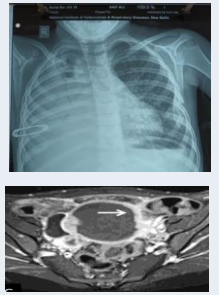
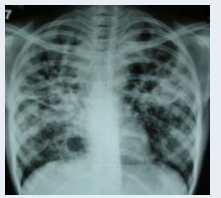
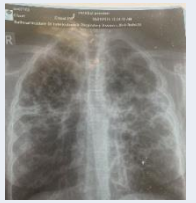
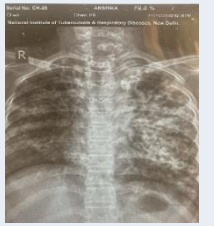
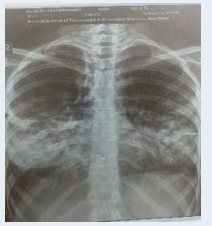
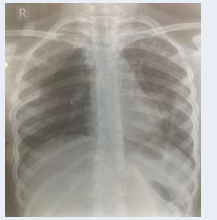
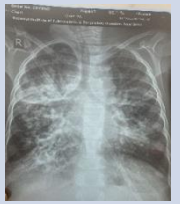
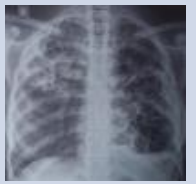
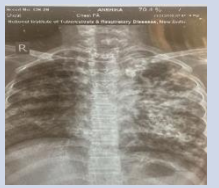
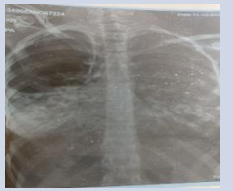
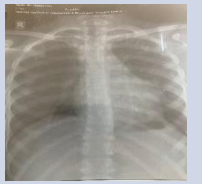
	Arm-I	Arm-II	Arm-III	Total N(%)
Bitter taste/spitting out	17	11	9	37(21)
Bulky quantity	17	12	11	40(22)
GI issues (vomiting, fullness, gastritis)	6	4	7	17(10)
Refusal to take medicines	0	1	0	1(0.5)

Most frequent challenges reported by caregivers were

- bulk of medicine(22%),
- bitter taste of tablet esp. with FQ (21`%),
- vomiting or spitting out of medicines (10%),
- Refusal to take medicines (0.5%) of Arm II despite counselling

# Death Summaries.
N=6/178 (3.37%)incl Fu.

# Treatment Outcome
N=5/178 (2.8%)

	Death-1	Death-2	Death-3	Death-4	Death-5	Death-6
Patient details	**S 14/F, Wt;30kg** Study ID : BC5320	**Z 9/F, Wt; 10 kg** Study ID : CC3130	**ZP 13/F** Study ID : BD2236	AC 14/F; Wt 26 kg Study ID: KH2366	RV 14/F; Wt 29 kg Study ID: HI3884	RI 17/F Wt 28kg;
Diagnosis	MDR PTB B/L Ext +EPTB (Pl. eff + CS +Abd +FGTB) 	MDR PTB B/L Ext + EPTB (CxLN +Abd) (Failure shorter MDR TB regimen + Cat-1) 	Probable MDR PTB B/L Ext PTB, (Failure of H mono resistant regimen) 	MDR PTB B/L Ext + EPTB (CxLN +Abd) 	Pre–XDR PTB 	Pre-XDR PTB (3+) 
Treatment given	ARM-I (BDQ+OBR)	ARM-I (BDQ+OBR)	ARM-I (BDQ+OBR)	Arm-II- DLM +OBR.	Arm-II(DLM+OBR)	ARM-III (BDQ+DLM+OBR)
Course in Hospital		GTCS (2Mo MRI Head Normal stabilized on Levetiracetam)		Failure to respond, shifted to Arm III, Anemia (Lzd stop),DIH,GTCS,Cardio (BDQ,DLM,Mfx,Cfz withheld)	DIH; Dlm with held	Anemia (Lzd stop) Cardio QTc 407 (T inver, STseg↑(V6) ?Anteroseptal MI (V3) (BDQ,DLM,Mfx,Cfz withheld)
Status	IP Ongoing	CP Ongoing	Cured	IP Ongoing Arm III	IP Ongoing	IP Ongoing
Timing of Death	D15 of treatment	11th Mo	Post treatment FU 1½mo	9 mo (2 mo Arm III)	D40	D10
Cause of death	QTc prolongation Respiratory failure Extensive disease	Respiratory failure Disseminated dis, SAM 	Sudden Pneumothorax 	SAE Sepsis, multi-organ failure 	Sudden death 	SAE 

Conclusion

- Preliminary results show that Longer Oral BDQ regimen appears to be effective, safe with good acceptability and retention followed by Shorter Combined BDQ + DLM based regimen.
- SAT or f-DOT is feasible, with strong therapeutic counselling and support, improved retention in care.

Strength:

- RCT
- Reasonable sample size with 3 comparative arms

Limitation:

- Ongoing study
- Final results awaited.
- Problem of patient retention for post treatment follow-up

Challenges faced:

Treatment monitoring

Intermittent stock out of child friendly formulations

Our team

Co- investigators

Dr. Manpreet Bhalla
Dr. Neeta Singla
Dr. RK Dewan
Dr. Ankita Dey, statistician

Dr. Pooja Chaudhary, JMO
Dr. Biswadip Saha, JR, NITRD
Dr Shashank Shastry, JR, NITRD
Mr. Sanjay Kumar, FW
Mr. Vikas Kumar, LT
Mr. Neeraj Kumar, DEO
Ms. Nikobo Singh, JRF

Thank You!