SURE trial update *and* challenges with recruitment and diagnosis

WHO child and adolescent TB annual meeting
14th November 2023, Paris

Julie Huynh

On behalf of the SURE trial team

Trial sponsor

Co-ordinating CTU

Funders (Global Health Trials Scheme)

Pk studies

Collaborating CTU

Collaborating study sites

SURE TRIAL team

MRC at UCL Trial management
Diana Gibb-Chief PI
Suzanne Anderson – Trial Physician
Anna Griffiths – Trial Manager
Caitlin Muller – Trial co-ordinator
Sierra Santana – Data manager
Angela Crooks – Main Statistician
Louise Choo – Statistician
Elena Frangou – Statistician
Robin Basu Roy – SURE DP lead
Susan Abarcar Salazar – SURE DP

TSC members
Independent
Victor Musime
Janet Darbyshire
Peter Donald
Vidya Mave
Sabine Verkuijl
Non-independent
Diana Gibb
Guy Thwaites
Hilda Mujuru
Varinder Singh

IDMC members
Tim Peto
Alwyn Mwinga
Katherine Fielding
Cheryl Hemingway

ERC
Steven Welch
Anna Turkova
Regan Solomons
James Seddon

OUCRU
Guy Thwaites – Co-PI
Evelyne Kestelyne – Head of CTU
Julie Huynh – Project Manager
Tran Bao Nguyen – Pharmacy
Thanh Thi Nguyen – CRC
Dai Minh Tran -CRC
Ny Thi Hong Tran – TB Study doctor
Tram Ngoc Pham –TB Study doctor
Thuy Thi Thanh Vo – TB Study nurse
Hiep Tuan Nguyen – TB Study nurse
Thu Dang Anh Do – TB Lab lead

University of Zimbabwe Clinical Research Centre (UZCRC)
Hilda Angeka Mujuru (PI)
Kusum Nathoo (Co-investigator)
Mutsa Bwakura (Co-investigator)
Ennie Chidziva (Trial manager)
Joyline Bhiri (Trial coordinator)
Sibususiwe Weza (Trial coordinator)
Misheck Phiri (Data Manager)
Godfrey Musoro (Clinician)
Vivian Mumbiro (Clinician)
Shepard Mudzingwa (Pharmacist)

Vietnam National Children's Hosp
Nguyen Van Lam – Site PI
Phan Huu Phuc – Site PI
Dao Huu Nam – Head ICU
Nguyen Phuong Hanh - Clinician
Nguyen Phuong Thao - Clinician

Children's Hospital 2
Trinh Huu Tung – Site PI
Do Chau Viet – Head ID ICU
Nguyen Dinh Qui – Head ID

National Lung Hospital
Nguyen Viet Nhung – Site PI
Nguyen Thi Hang – Head Paediatrics
Pham Dinh Dong – Clinician

Post Graduate Institute of Education and Medical Research
Naveen Sankyan (PI)
Titiksha Sirari (Project Scientist)
Anju C (Research nurse)
Diksha Pathania (Pharmacist)

Kalawati Saran Children's Hospital
Varinder Singh (PI)
Suvasini Sharma (Co-investigator)
Yogesh Kumar Tiwari (Trial coordinator)
Komal Rani (Staff Nurse)
Karan Kumar (Pharmacist)
Viskas Goswani (Data entry officer)

Makere University –John Hopkins Uni
Eric Wodudeya (PI)
Sabrina Kitaka (Co-PI)
Mark Ssenyonga (Pharmacist)
Emmanuel Mayanja (Data technician)
Donald Wagaana (Data technician)
Winnie Nansamba (Data Manager)
Nancy Nabukerra (Clinician)

University Teaching Hospital, Zambia
Chisala Chabala (PI)
Joyce Chipili Lungu (Trial coordinator)
Lisa Nkole (Trial Clinician)
Veronica Mulenga (Co-investigator)
Terence Chipoya (Data-manager)
Friday H Mwanakalanga (Data-manager)
Susan Zulu (Research nurse)
Bwalya Simunyola (Pharmacist)

Pham Ngoc Thach Hospital
Nguyen Thi Hong Nhung – Site PI
Cuong Hung Pham (Pharmacist)

Shorter intensified anti-tuberculosis therapy for children with TBM?

WHO-recommended regimen 2HRZE/ 10HR

- Long treatment
- Poor penetration of R and E into CSF
- After 2 months only H is in CSF
- No effective drugs in H-resistant TB

Emerging evidence

- Higher doses R associated with quicker culture conversion in PTB
- Intensified treatment with 4 drugs given for ***6 months*** may be at least as effective
- Fluoroquinolones may have a place in regimen

1. Diacon et al. Antimicrob Agents Chemother 2007
2. Heemskerk et al. Clin Infect Dis 2017
3. Sulis et al. OFID 2021

Shorter intensified anti-tuberculosis therapy for children with TBM?

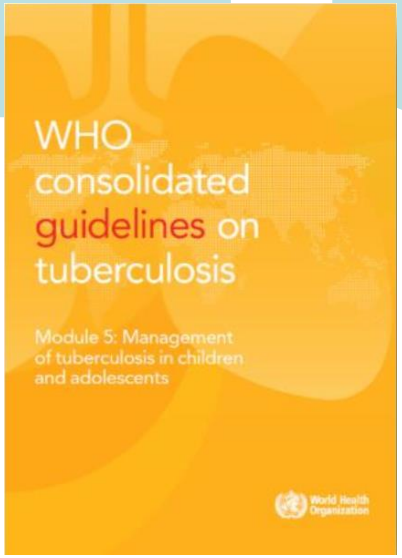
WHO-recommended regimen 12 months

H 7-15 mg/kg, max 300mg
R 10-20 mg/kg, max 600mg
Z 30-40 mg/kg
E 15-25 mg/kg

'Cape Town regimen' 6 months

H 20 mg/kg, max 400mg
R 20 mg/kg, max 600mg
Z 40 mg/kg, max 2g
Ethionamide 20mg/kg, max 750mg

Strong recommendation
Low quality of evidence



Conditional recommendation
Very low certainty of evidence

Shortened intensified anti-tuberculosis therapy for children with TBM?

WHO-recommended regimen 12 months

H 7-15 mg/kg, max 300mg
R 10-20 mg/kg, max 600mg
Z 30-40 mg/kg
E 15-25 mg/kg

'Cape Town regimen' 6 months

H 20 mg/kg, max 400mg
R 20 mg/kg, max 600mg
Z 40 mg/kg, max 2g
Ethionamide 20mg/kg, ma

Modified 'Cape Town regimen' 6 months = SURE trial

H 20 mg/kg, max 400mg
R 30 mg/kg, max 600mg
Z 40 mg/kg, max 2g
Levofloxacin 20mg/kg, max 1g

Host directed therapy – adjuvant aspirin?

PHASE 2 RCT

- **HIV neg adults with TBM**

Placebo vs **Aspirin 81mg vs 1000mg**

(8 week duration)

- in addition to SOC

MAIN FINDINGS

- ↔ in **grade 3/4 bleed** or **deaths/new infarcts**

- Subanalysis: ↓ deaths/infarcts in aspirin treated with confirmed TBM

ANCILLARY FINDINGS

- High dose aspirin assoc. with

Better resolution infarcts

CSF: ↓**inflammatory** mediators + ↑**pro-resolving** mediators

Mai et al. elife 2018

SURE trial questions

Is 6 months of intensified ATT as good as the 12-month standard for TBM?

AND

Does high-dose aspirin improve neurofunctional outcomes in children with TBM?

SURE trial design

A phase III, multi-centre, international, partially-blinded **factorial randomised controlled trial** of TBM treatment in children

Factorial trial: all patients enter the two randomisations 1, 2 simultaneously

Anti – tuberculosis

1 **RANDOMIZATION – OPEN LABEL**

1:1

Intensified **6-month** Arm ($6H^{HD}R^{HD}ZL$)	Standard **12-month** Arm (2HRZE 10HR)

H=isoniazid, R= rifampicin, Z=pyrazinamide, L=levofloxacin, E=ethambutol, ^{HD}=high-dose

Anti –inflammatory

2 **RANDOMIZATION – DOUBLE BLIND**

1:1

Aspirin 20mg/kg for 8 weeks	**Placebo** for 8 weeks

Total follow-up 72 weeks for each patient

+

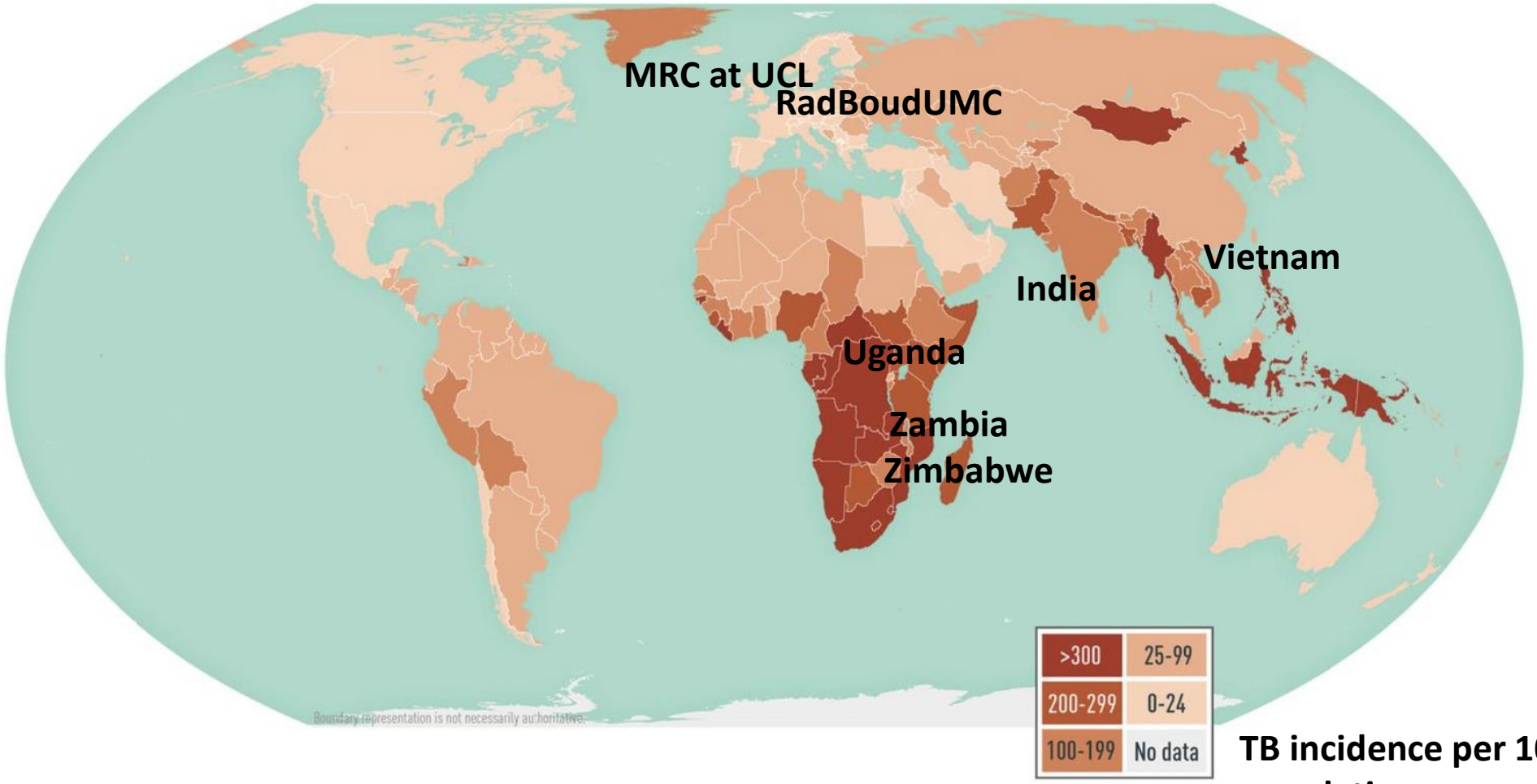
Non-trial treatment required for ALL patients

1. Corticosteroids for 8 weeks (SOC)
2. Ranitidine prophylaxis for 8 weeks (Prevention of the bleeding risk of Aspirin)

Children aged between 29 days and under 18 years with TBM disease, with or without HIV infection

N = 400

SURE trial sites



TB incidence per 100,000 population

CDC yellow book 2023

SURE trial design

A phase III, multi-centre, international, partially-blinded factorial randomised controlled trial of **TBM treatment in children**

POPULATION

Children aged between 29 days and under 18 years with TBM disease, with or without HIV infection

N = 400

PATIENT INCLUSION CRITERIA

1. Age
2. Weight: ≥3kg
3. Parent/legal carer giving informe consent
4. Agree for a CSF sample to be collected and processed
5. Diagnosis:
   - Symptoms compatible with TBM

   and/or
   - CSF result with abnormalities compatible with TBM

PATIENT EXCLUSION CRITERIA

1. Resistance to rifampicin
2. On ATT for >21 days

5. Specific medical history:
   - Known allergy or other contraindication to icosteroids, or aspirin
   - ng diathesis
   - conditions:
   - n with influenza or
   - ns

SURE trial design

1 RANDOMISATION 1 – Open Label

Intensified **6-month** ATT Treatment
($6H^{HD}R^{HD}ZL$)

Non-inferior?*

Standard **12-month** ATT Treatment
(2HRZE 10HR)

PRIMARY OUTCOMES

All-cause mortality at 48 weeks

***Detect 10% non-inferiority** assuming mortality of 20% in control arm and 3% absolute reduction

SURE trial design

2 RANDOMISATION 2 – Double Blind

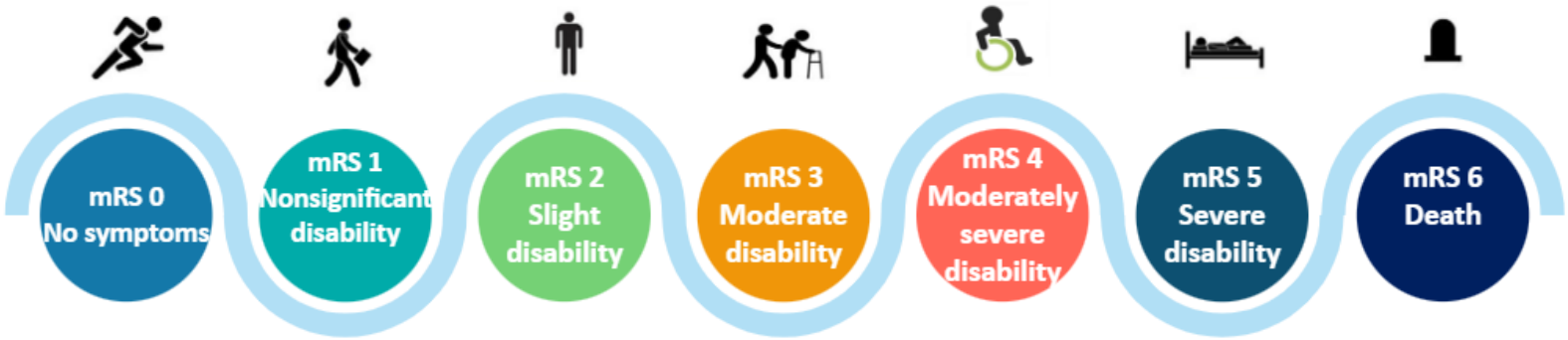
Aspirin 20mg/kg for 8 weeks

Superior?*

Placebo for 8 weeks

PRIMARY OUTCOMES

Modified Rankin Scale (mRS) measuring functional outcome at 48 weeks



The paediatric Modified Rankin Scale

*__Detect 16% superiority__ assuming mortality and disability of 50% in placebo arm.

SURE trial design

1 RANDOMIZATION 1 – Open Label

Intensified **6-month** ATT Treatment (6HRZL)

Non-inferior?

Standard **12-month** ATT Treatment (2HRZE 10HR)

2 RANDOMIZATION 2 – Double Blind

Aspirin 20mg/kg for 8 weeks

Superior?

Placebo for 8 weeks

SECONDARY OUTCOMES

1) **mRS outcomes** at W24, W48 (for randomisation 1) and W72

2) **All-cause mortality** at W72

3) Clinical or microbiological **relapse of TBM and/ or TB disease** by W72

4) **Specific adverse events (AEs):**

- Any new Grade 3 and Grade 4
- Leading to treatment modification (any grade)
- Any gastrointestinal bleeding (any grade)
- Drug-induced liver injury (DILI) of Grade 2 or more
- Development of obstructive hydrocephalus

6) **Acquired drug resistance**

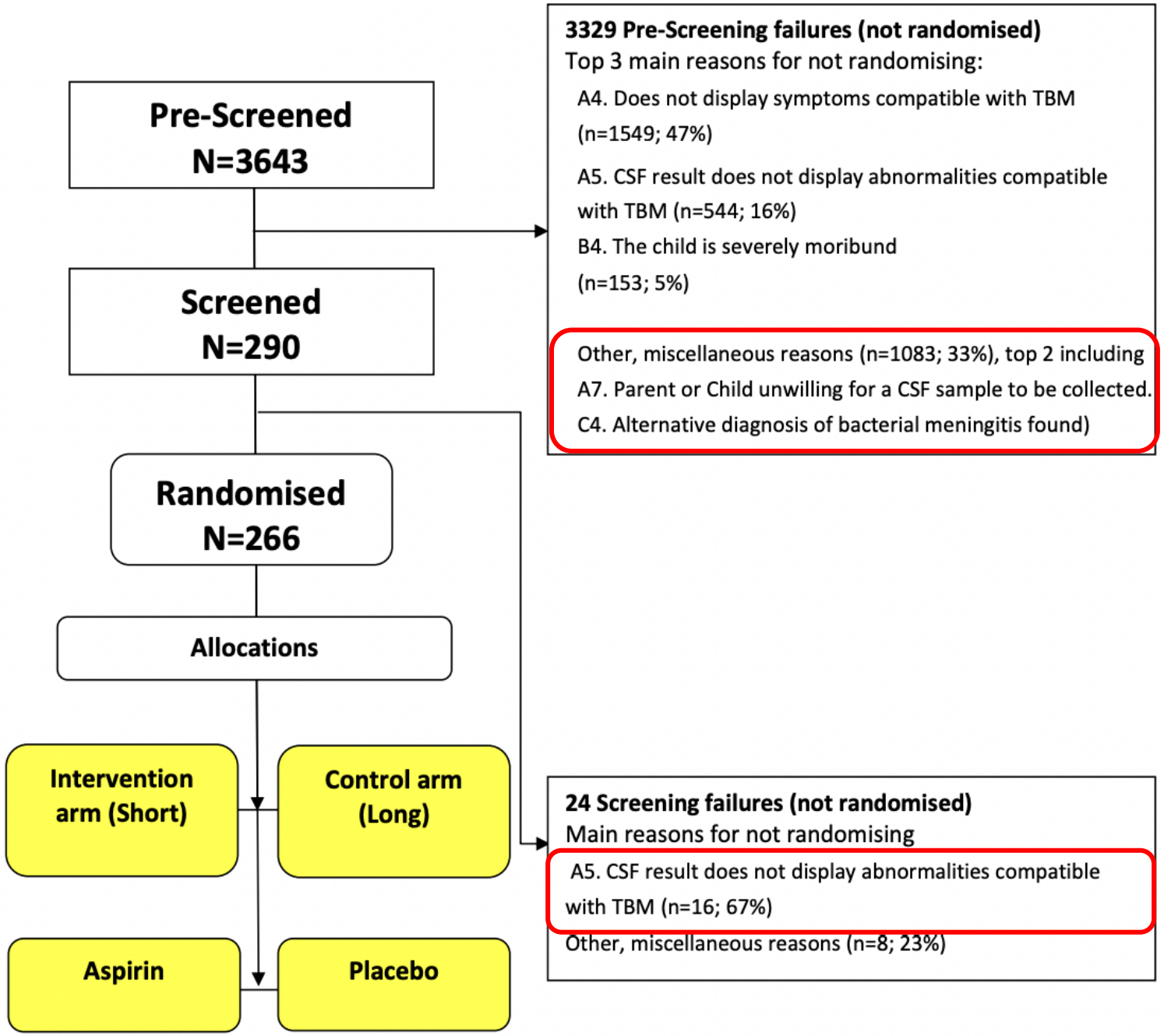
7) **Adherence** to treatment

8) **Acceptability** to treatment

9) Assessment of **HIV viral load** for HIV patients

Enrolment

***Preliminary Data:**
1st Oct 2023 data extraction



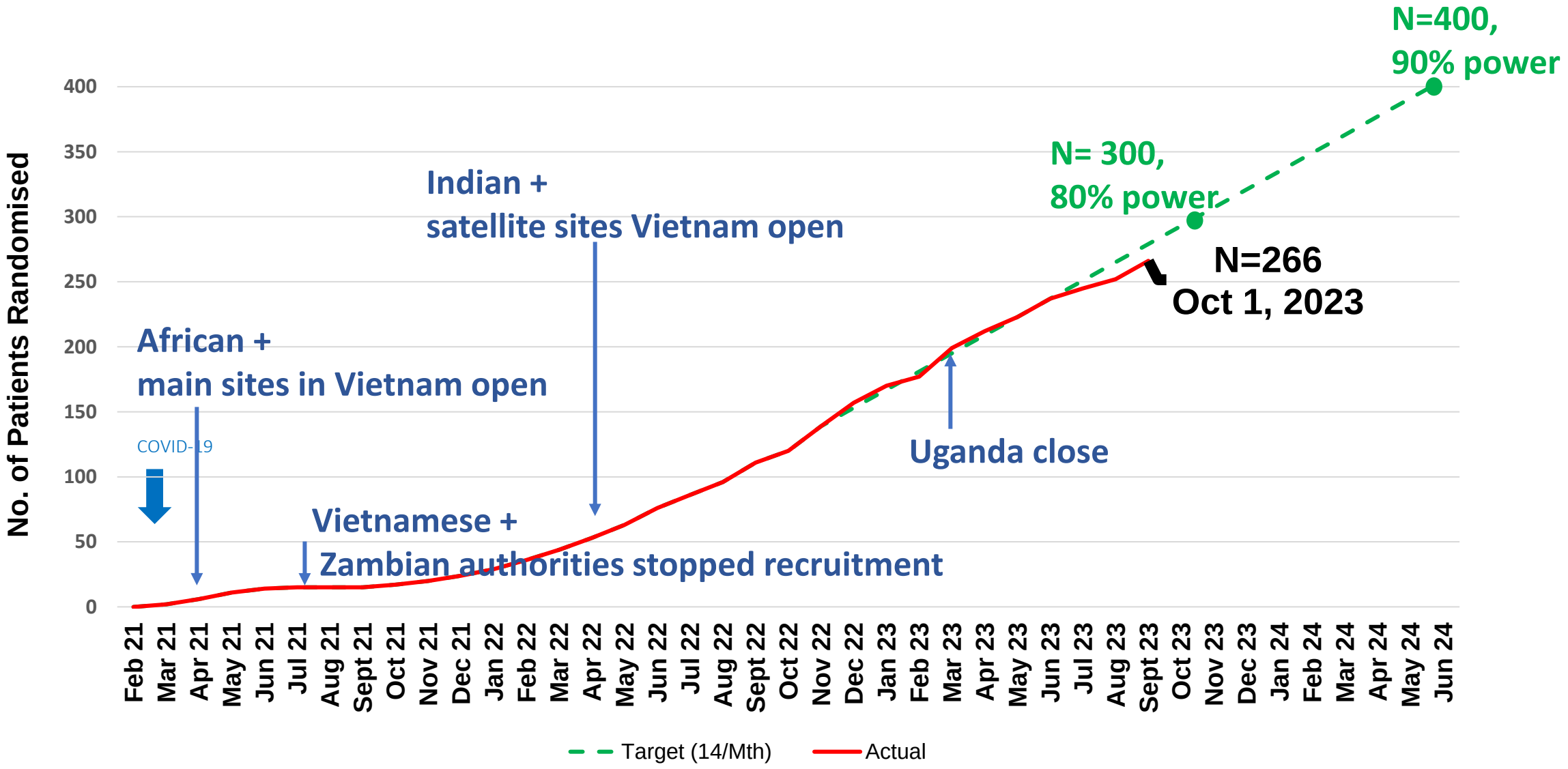
Total participants randomised by centre

Country	India		Vietnam				Uganda	Zambia	Zimbabwe	Total
No. randomised	90		120				2	31	23	**266**
Site name	**PGI Chandigarh**	**LHH Delhi**	**PNTH HCMC**	**CH2 HCMC**	**NLH Hanoi**	**VNCH Hanoi**	**MU-JHU Uganda**	**UTH Zambia**	**UZCRC Zimbabwe**	
Date site opened to recruit	11/02/22	25/03/22	22/02/21	01/06/22	19/04/21	13/06/22	07/04/21	19/03/21	22/02/21	
No. randomised by site	**40**	**50**	**67**	**26**	**13**	**14**	**2**	**31**	**23**	**266**

VNCH: Vietnam National Children's Hospital
UZCRC: University of Zimbabwe Clinical Research Centre
MU-JHU: Makerere University – Johns Hopkins University
PGI: Post Graduate Institute of Education and Medical Research
LHH: Lady Hardinge Hospital (Kalawati Saran Children's Hospital)

CH2: Children Hospital 2
NLH: National Lung Hospital
PNTH: Pham Ngoc Thach Hospital
UTH: University Teaching Hospital

SURE Recruitment - All Sites

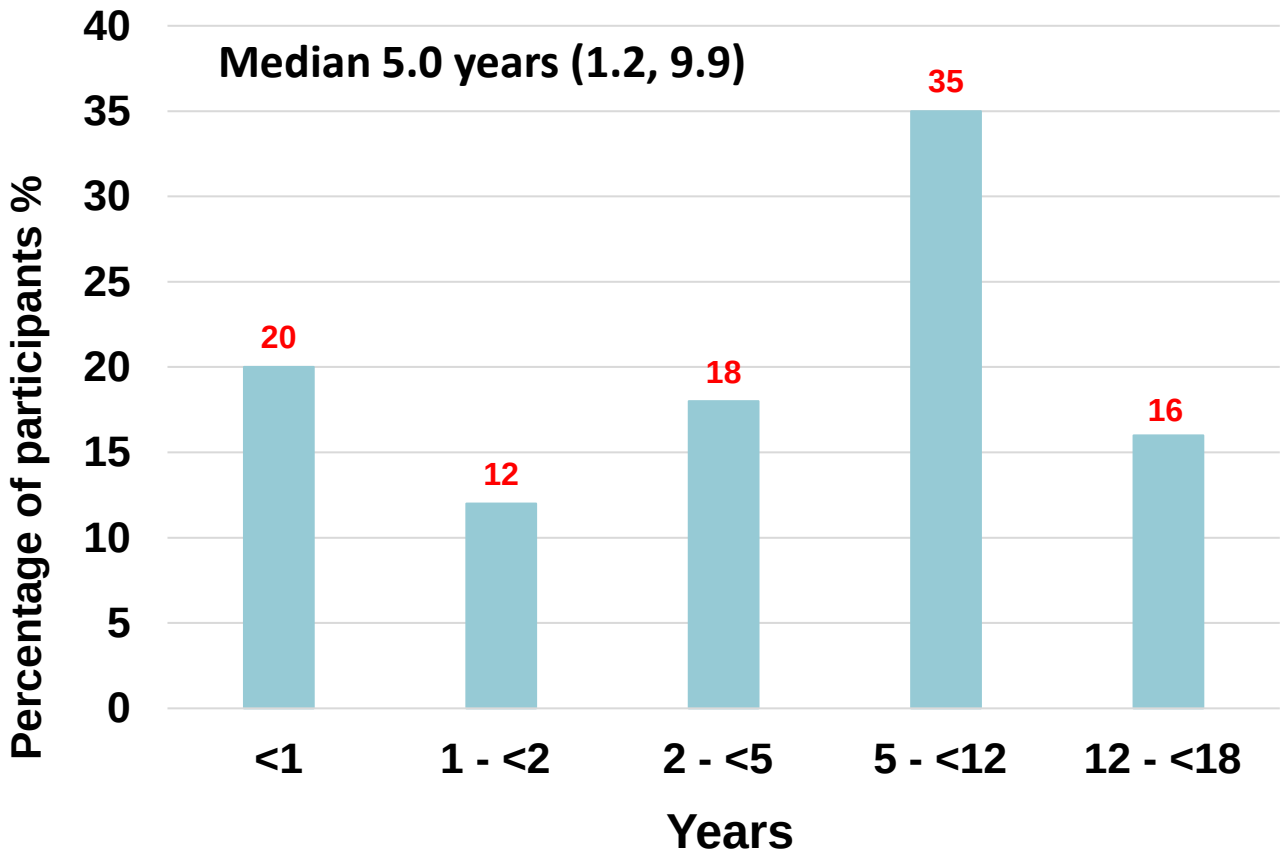


Participant retention

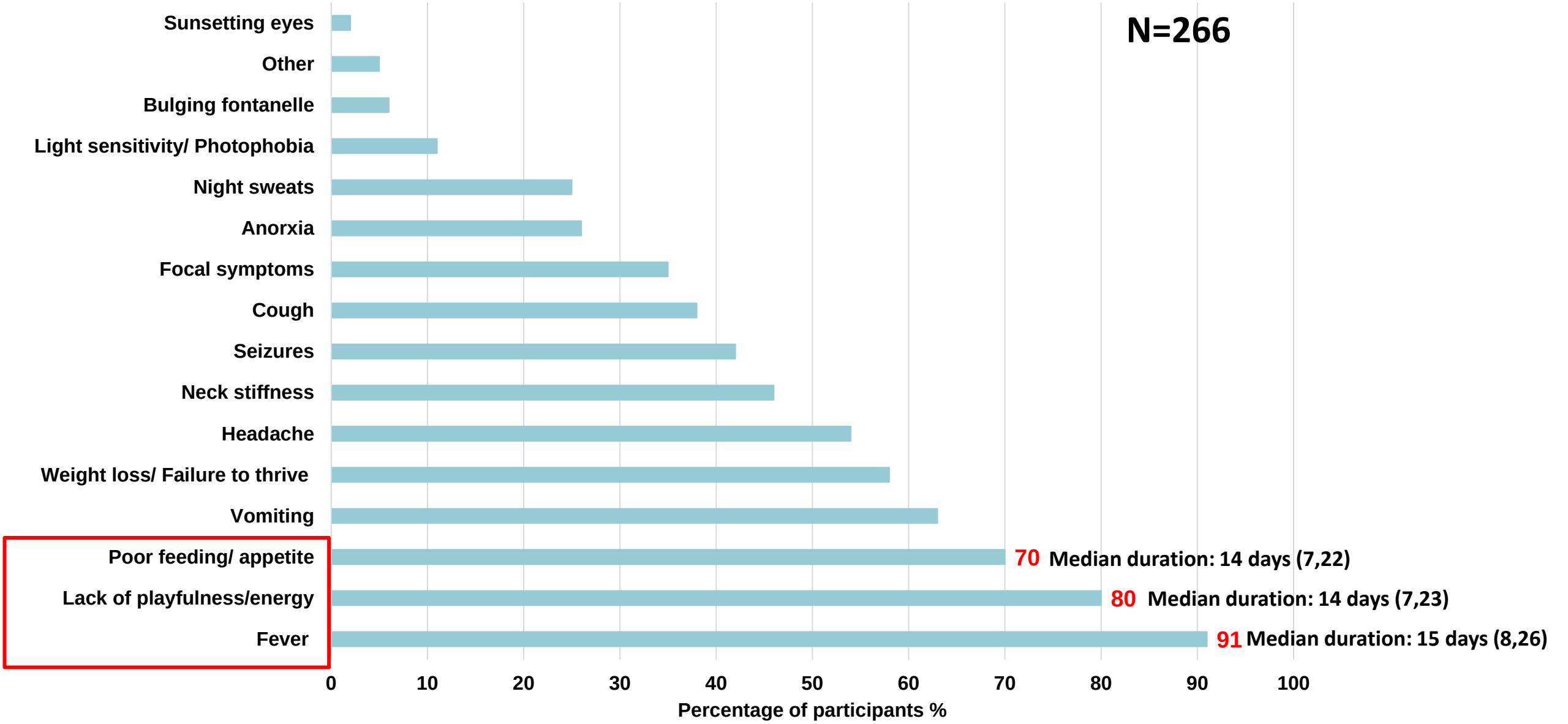
Visit	India	Uganda	Zambia	Zimbabwe	Vietnam	Total
No. Randomised	90	2	31	23	120	**266**
Week 48 *Attendance /Expected*	24/25	1/1	12/12	2/2	54/55	**93/95 (98%)**
Week 72 *Attendance/ Expected*	3/4	1/1	8/8	1/1	26/29	**40/43 (93%)**

Demographics

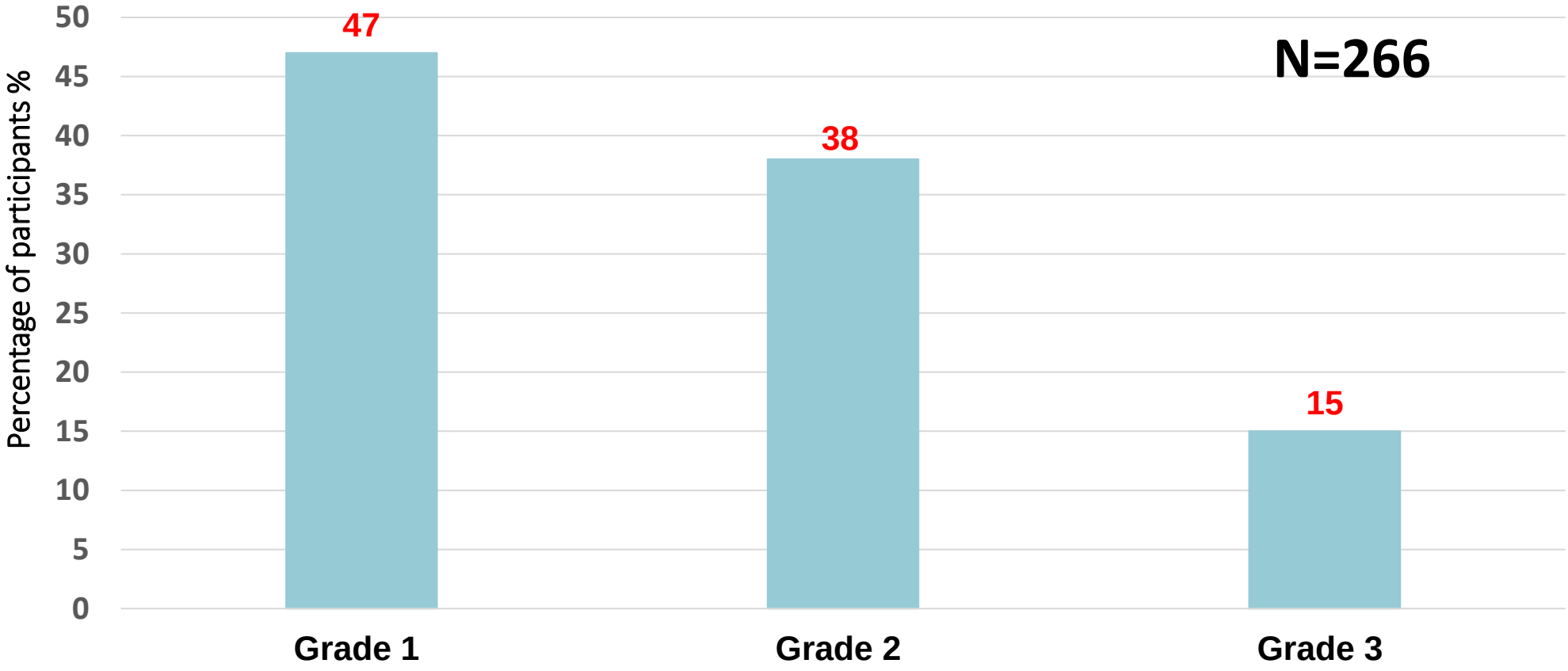
No. randomised = 266		
Gender	Male	144 (54%)
	Female	122 (46%)
HIV status	Negative	252 (95%)
	Positive	12 (5%)
	On ART at randomisation	2



Baseline TBM Symptoms



TBM Staging


Percentage of participants %
50
45
40
35
30
25
20
15
10
5
0
47
38
15
N=266
Grade 1
Grade 2
Grade 3

TB Microbiology

N = 266	Smear	GeneXpert/ GeneXpert Ultra	MGIT culture
No. Patients with sample collected	256	249	212
No. with MTB detected/ with results	43 / 224 * (17%)	110 / 249 ** (34%)	46/212 *** (22%)

* 76% positive on CSF / CSF + respiratory, 24% negative on CSF negative but positive elsewhere

** 80% positive on CSF / CSF + respiratory, 20% negative CSF negative but positive elsewhere

*** 85% positive on CSF / CSF + respiratory, 15% negative on CSF negative but positive elsewhere

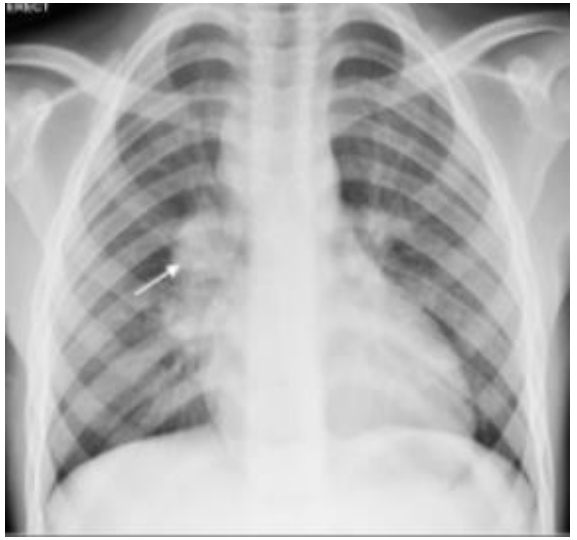
Chest X-Ray (CXR)

No. Baseline CXR		248
CXR result	Abnormal	125 (54%)
	Normal	106 (46%)
	Missing	17

Typical of TB	82 (66%)
Not typical of TB	43 (34%)

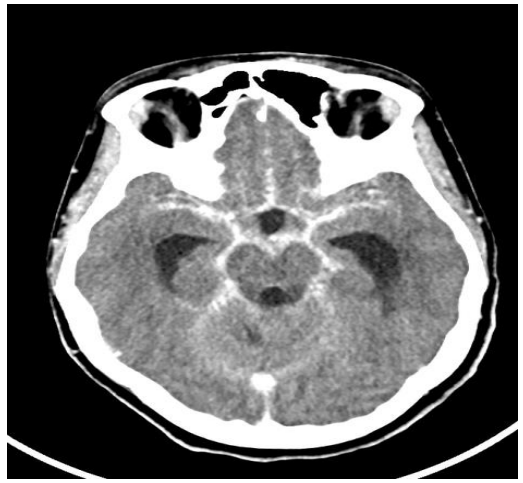
Most common abnormalities

1. **Uncomplicated lymph node disease (35%)**
2. **Miliary TB (26%)**
3. **TB Bronchopneumonia (14%)**



Right hilar lymphadenopathy

Cerebral imaging

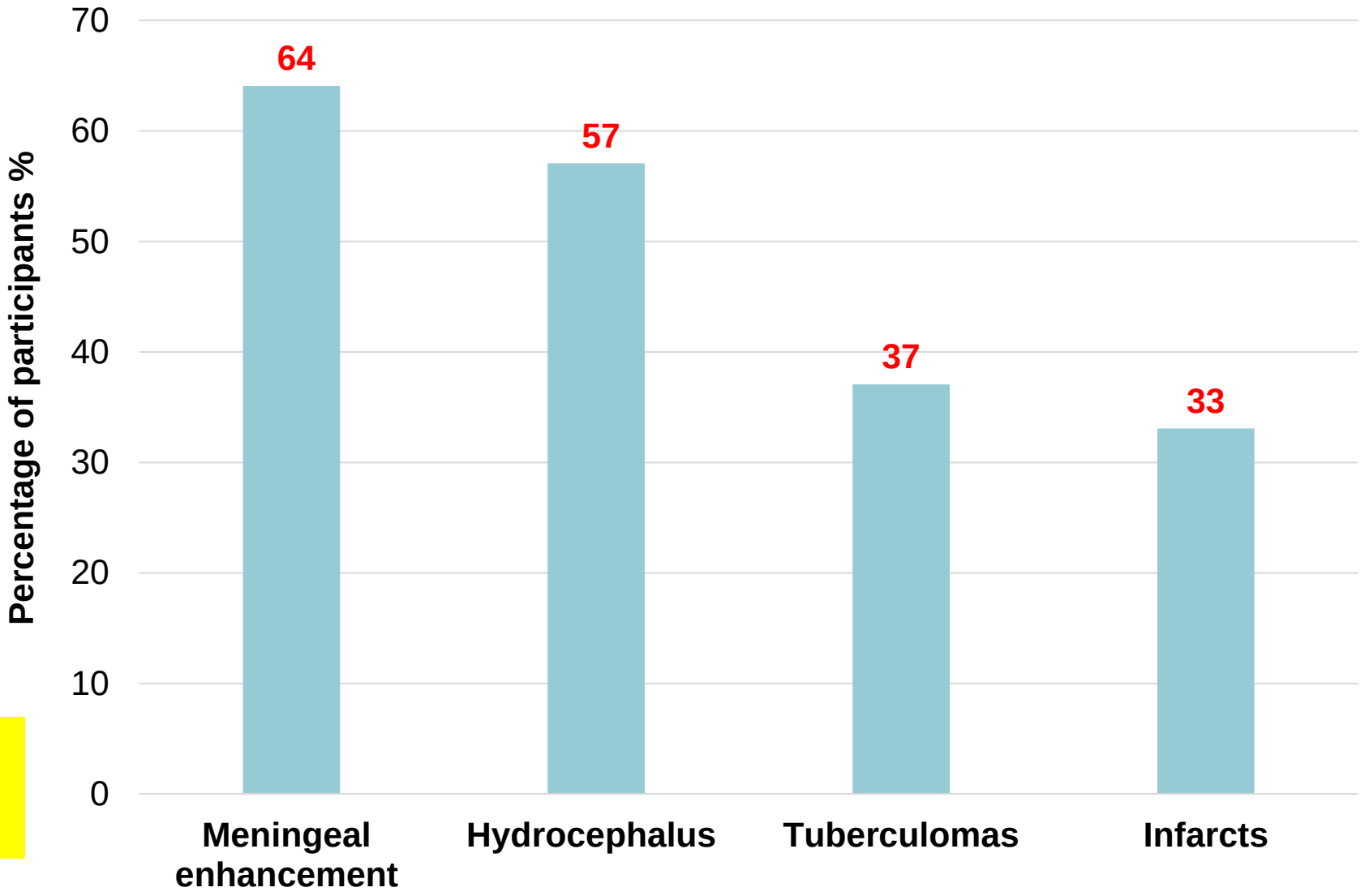


N=189

138 MRI

51 CT

171(90%) abnormal
18 (10%) normal



Baseline TBM Categorisation

No. Randomised	266
No. with Baseline TBM Categorisation	257 *
Definite	101 (39%)
Probable	93 (36%)
Possible	61 (24%)
Not categorised	2 (1%) **

* 9 cases not classified (pending further information, pending queries or CSF Score=0 & No Imaging)
** No CSF

*Marais S, Thwaites G, Schoeman JF, et al. Tuberculous meningitis: a uniform case definition for use in clinical research. Lancet Infect Dis **2010**; 10:803–12*

Diagnostic challenges and opportunities

CHALLENGES

- LP refusal by parents and staff
- Limited CSF microscopy skill, delayed processing
- Diagnosis dependent on clinical; junior staff with limited experience
- Early diagnosis is difficult, ideally MRC grade 1 when benefit (if any) is most likely

OPPORTUNITIES

- Animated video on LP procedure for parent/carer

https://www.picturinghealth.org/lumbar-puncture/

Led by Susan Abarcar Salazar

- LP education and practical workshops
- Diagnostics substudy which recruited controls desensitised parents to LP
- Unexpected TBM cases captured through diagnostics substudy

Explaining LP: A guide for parents in Africa
https://vimeo.com/638617138

SUMMARY

- SURE trial is the largest TBM trial in children and adolescents
- Challenging diagnosis, < 35% identified on rapid molecular diagnostics on CSF
- Diagnostic substudy embedded in trial augmented participant recruitment
- 75% of children with confirmed and probable TBM
- Half of children affected by TBM were < 5 years
- More than 50% of children enrolled have moderate–severe disease
- Reached 70% of target recruitment, complete recruitment Jun 2024, end follow up Dec 2025

Susan Abarcar Salazar

Peruvian Infectious Diseases Specialist

PhD candidate (London School Hygiene and Tropical Medicine)

SURE trial management group member

Daughter, sister, aunty, friend