Comparison of single versus combination drug therapy in extensively drug-resistant Salmonella Typhi in terms of time to defervescence: A randomized controlled trial

[Document subtitle]

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Comparison of single versus combination drug therapy in extensively drug-resistant Salmonella Typhi in terms of time to defervescence: A randomized controlled trial

By

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For

MD Pediatrics

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To

The Vice Chancellor,
University of Health Sciences,
Lahore

Subject: **SUBMISSION OF REVISED SYNOPSIS**

This response is in reference to the observations made by the Synopsis Review Committee for the synopsis titled **Comparison of single vs combination drug therapy in extensively drug-resistant Salmonella typhi in terms of time to defervescence: A Randomized Controlled Trial** submitted for MD (Pediatrics) vide letter no.UHS/DPS-26/113 dated 15/01/2026.All the observations have been carefully addressed and an overview of the corrections made has been listed below:

Observations	Amendments/Remarks
Dose of Meropenem must be mentioned.	Dose of meropenem added that is 20-40mg/kg/dose every 8 hourly.
Disease severity criteria shall be added in the synopsis.	Disease severity criteria has been included in the synopsis on page no.10.
Management during observation period must be mentioned in the methodology.	Management during observation period has been mentioned on page no.15.
Operational definition of XDR must be written.	Operational definition of XDR enteric fever added on page no.10.
Sampling technique shall be simple random sampling.	Sampling technique has been corrected to simple random sampling on page no.12.
CONSORT guidelines must be followed and it must be registered.	The study will follow consort guidelines and has been registered at ClinicalTrials.gov.
Normality testing and non-parametric testing must be added.	Normality testing and non-parametric testing has been added on page no.16.
Formatting must be on UHS guidelines.	Formatting has been revised according to UHS synopsis guidelines including headings, spacing, referencing style.
In text citations shall be added and references shall be on Harvard style.	All references have been rewritten in Harvard style and in text citations have been added throughout the synopsis.
Dr. Sobia Qamar **(Supervisor)**	
Prof. Dr.Agha Shabbir Ali	

UNIVERSITY OF HEALTH SCIENCES, LAHORE

SYNOPSIS PROFORMA

Title of Research Project: **Comparison of single vs combination drug therapy in extensively drug-resistant Salmonella typhi in terms of time to defervescence: A Randomized Controlled Trial**	
Synopsis submitted for: Master of Medicine (MD)	Discipline: Pediatric Medicine
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Worked as a Medical Officer in the Tertiary care department for 5 months

Name of post-graduate institution currently studying.

Children's Hospital and Institute of Child Health Sciences, Lahore.

Prof. Dr. Date:

Signature

: (Academic Supervisor)

Prof. Dr. Signature: Date:

(Head of Department)

Prof. Dr. Masood Sadiq Signature: Date:

(Vice Chancellor)

Convener, Ethical Review Committee Signature: Date:

Chairman (Advanced Studies & Research Board) Signature: Date:

☐ Approved ☐ Not Approved

Vice Chancellor, UHS

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List of Abbreviations

ESBL	Extended-Spectrum β-Lactamase
IV	Intravenous
MMIDSP	Medical Microbiology and Infectious Diseases Society of Pakistan
SPSS	Statistical package for social sciences
WHO	World Health Organization
XDR	Extensively Drug-Resistant

PROJECT SUMMARY

Typhoid fever is one of the many diseases that burden third-world countries among children. Recent data shows that typhoid fever is very common in developing countries, along with an estimated 120 million infections and 700,000 annual deaths occurring worldwide. Although improved water quality and sanitation constitute ultimate solutions to this problem, vaccination in high-risk areas is a potential control strategy recommended by the World Health Organization (WHO) for the short- to medium-term management. This study aims to compare the treatment outcome between those who will receive single drug therapy (meropenem) versus combination drug therapy (azithromycin plus meropenem).

Regardless of increasing use of combination drug therapy in XDR typhoid fever there is limited evidence of randomized controlled trial of comparing time to defervescence between single and combination drug therapy. We aim to contribute to the existing guidelines on managing this prevalent and difficult-to-treat infection. A total of 94(47 in each group) patients meeting the selection criteria will be enrolled in this study. Single-drug therapy will be defined as patients who will receive carbapenem (meropenem), and combination-drug therapy will be carbapenem plus azithromycin. Patients will receive carbapenem intravenously (IV) at a dose of 30 mg/kg/dose every 8 hours (maximum 2g per dose) and azithromycin (oral) at 20 mg/kg/day according to the hospital protocol. Defervescence and time to defervescence will be noted. All the data will be entered in SPSS v25.0. An Independent sample t-test or Mann-Whitney U test will be used depending upon the data distribution to compare the hospital stay and time to defervescence between groups. The chi-square test will be used to compare the defervescence and complications between groups. A p-value ≤ 0.05 will be taken as significant.

INTRODUCTION:

Typhoid fever is a systemic infection caused by Salmonella enterica serovar Typhi (S. Typhi). Typhoid fever presents a significant challenge in low- and middle-income countries, with around 20 million cases and 161,000 deaths reported annually. The disease causes high fever, abdominal pain, and headaches, impacting individuals' quality of life. Without treatment, it can lead to severe complications such as intestinal hemorrhage and perforation, increasing mortality rates. Timely diagnosis and medical intervention are crucial to manage typhoid fever and reduce its impact on health effectively (Bhutta et al., 2018; Kaluse et al., 2021).

In the mid-1980s, Salmonella typhi became more resistant to common typhoid fever treatments like chloramphenicol, ampicillin, and trimethoprim. This rise in multi-drug-resistant strains caused widespread outbreaks in regions including the Indian subcontinent, Southeast Asia, and Africa, creating significant public health concerns. By 2014, reports showed sporadic resistance, even to third-generation cephalosporin, escalating global fears about drug-resistant strains spreading (Zakir et al., 2021; Ahsan and Rahman, 2019)

In November 2016, an epidemic of ceftriaxone-resistant typhoid fever broke out in Hyderabad, Pakistan, caused by Salmonella typhi 4.3.1 (H58) clade. This strain is extensively drug-resistant, posing a grave public health threat and highlighting the urgent need for advanced surveillance and intervention strategies. The emergence of highly resistant typhoid strains emphasizes the complexity of antimicrobial resistance dynamics, prompting a comprehensive approach involving antimicrobial stewardship, infection control, and innovative treatment research to address this escalating crisis. *(Akram et al., 2020; Klemm et al., 2018)*

A strain with the blaCTX-M-15 gene, causing resistance to ceftriaxone, was discovered in XDR typhoid. It has spread to urban areas in Sindh, notably Karachi. Around 20,000 confirmed cases have been reported in Hyderabad and Karachi by August 2021, highlighting the escalating public health crisis (Klemm et al., 2018)

Since 2018, numerous XDR typhoid cases have surfaced globally, originating from the H58

lineage in Pakistan. This lineage, with superior competitive abilities and international travel-based transmission, has caused outbreaks in the United States, England, Canada, and China. The discovery underscores the pandemic threats posed by a single strain capable of crossing borders and endangering global public health (Klemm et al., 2018; Wang et al., 2022)

Azithromycin is a type of macrolide antibiotic that fights bacterial infections by targeting and disrupting the bacterial ribosome, specifically the 50S large ribosomal subunit[15], [16].Although it primarily inhibits bacterial growth, azithromycin is considered bacteriostatic, meaning it slows down or stops bacterial proliferation rather than killing the bacteria outright. This allows the immune system to more effectively combat the infection. Azithromycin is effective against a variety of bacteria, including both Gram-positive and Gram-negative organisms, as well as some atypical pathogens like Chlamydia, Mycoplasma, and Legionella (Oliver and Hinks, 2021).

Meropenem is a type of carbapenem carboxylic acid that works by inhibiting bacterial cell wall synthesis. It binds to penicillin-binding proteins (PBPs) on the bacterial cell wall, which are essential for cell wall biosynthesis. By binding to these PBPs, meropenem prevents the cross-linking of peptidoglycan layers in the bacterial cell wall. This disruption leads to cell lysis and death. Meropenem is effective against a wide range of Gram-positive and Gram-negative bacteria, including many strains resistant to other antibiotics. It also covers some anaerobes (Steffens et al., 2021).

Managing extensively drug-resistant (XDR) typhoid is challenging due to limited treatment options. In 2019, the MMIDSP developed guidelines based on antimicrobial susceptibility profiles, recommending azithromycin and carbapenem to treat XDR typhoid, with a focus on improving patient outcomes and controlling drug resistance (Hussain et al., 2019).

Further research is required to assess patient outcomes after treatment with limited antibiotics, specifically single versus combined therapy. Qureshi et al.'s study found no significant difference in effectiveness between the two approaches. This emphasizes the need to consider both economic factors and treatment efficacy when determining the best antibiotic therapy for patients (Qureshi et al., 2020).

Literature Review:

Typhoid fever, which is induced by the bacterium S. typhi, is known to be curable; however, its chronicity is often attributed to the intricacies of its pathogenesis and the resemblance of its symptoms to those of malaria. Despite being a relatively uncommon ailment in more advanced nations, the prevalence of typhoid fever remains a significant concern in less developed regions as a result of inadequate access to safe drinking water, substandard environmental hygiene, and poor food safety practices. The combination of these factors facilitates the transmission of the disease, making it a considerable public health issue in developing countries (Elven et al., 2020,Meiring et al., 2021,Umair and Siddiqui, 2020))

In research conducted by Ishaque et al., it was observed that among the 254 patients included in the study, a majority of 179 individuals, equivalent to 70%, were identified as male with an average age of 11.7 ± 10.9 years. Moreover, a significant portion of about 190 patients, accounting for 74% of the total, underwent treatment involving combination therapy.

Specifically, 126 patients, which makes up 49% of the sample, were administered a combination of azithromycin and meropenem, while 61 patients, constituting 24%, received a combination of azithromycin and imipenem. Furthermore, the study revealed that a total of 64 patients, representing 25%, received single drug therapy, with 33 individuals (12%) prescribed azithromycin, 23 patients (9%) given meropenem, and 8 individuals (3%) treated with imipenem.

Analysis revealed that the utilization of a single drug for therapy led to an earlier commencement of defervescence when contrasted with employing a combination of drugs (5.03±2.98 days versus 3.45±2.48 days; $p<0.001$). Moreover, this approach was associated

with a reduced incidence of pancytopenia ($p<0.001$). It was observed that the initiation of defervescence was achieved sooner with the administration of a single antimicrobial therapy in comparison to combination therapy, particularly highlighting the superior performance of carbapenems over azithromycin (Ishaque et al., 2022).

In a separate investigation conducted by Qureshi and colleagues, a comprehensive analysis was carried out on the medical records of 81 individuals diagnosed with extensively drug-resistant (XDR) typhoid who were admitted to the Aga Khan University (AKU) hospitals. Among the cohort, the majority (n = 45; 56%) were identified as male, while the mean age of the patients stood at 8.03 years, ranging from 1 to 40 years. A significant proportion of the patients, amounting to about three quarters of the total (n = 66), received inpatient care during their treatment regimen. Notably, fever and vomiting emerged as the prevailing symptoms observed at the time of initial presentation in these cases.

The therapeutic strategies employed included the administration of oral azithromycin alone (n = 22; 27%), intravenous meropenem alone (n = 20; 25%), or a combination of azithromycin and meropenem (n = 39; 48%). The average time required for defervescence, as indicated by the 95% confidence interval, was recorded at 7.1 (5.5– 8.6) days for azithromycin, 6.7 (4.7–8.7) days for meropenem, and 6.7 (5.5–7.9) days for the combined treatment approach. Importantly, there were instances of treatment failures within the respective options, with 1, 0, and 3 failures reported for azithromycin, meropenem, and the combination therapy, respectively. These findings shed light on the diverse treatment modalities and outcomes observed in XDR typhoid patients, underscoring the need for further research to optimize clinical management strategies in such cases.

Patients who have been administered either Azithromycin, Meropenem alone, or a combination of the two exhibited comparable durations until defervescence. The utilization of this observational data allows for the establishment of background estimates essential for conducting power calculations to ensure the robustness of future clinical.

In a study, Iftikhar et al. found that among the risk factors, features like severe abdominal pain, diarrhea, hepatosplenomegaly, leucopenia, thrombocytopenia, severe anemia, and poor socioeconomic status were more commonly seen in patients with complicated enteric fever admitted in our setup. So, the presence of these factors may suggest higher chances of developing complications in children with enteric fever (Iftikhar, Hamid and Masood, 2019). This data provides a valuable foundation for enhancing the methodological rigor and statistical power of clinical research endeavors in healthcare (Qureshi et al., 2020) .

In another study done by Iftikhar et al., noted that out of 180 patients, complications were noted in 58 (32.2%). Neurological complications 30.7% encompassed maximum complications, followed by hepatobiliary 24.61%, abdominal 16.92%, hematological 9.23%, bone and joints 7.69%, respiratory system 6.1%, and cardiovascular system 4.41%. The mortality rate was 1.6%. Thrombocytopenia and leucopenia were significantly associated with complications, with p-values of 0.002 and 0.003, respectively. Enteric fever is causing our children to suffer from its numerous perplexing and fatal complications. The most vulnerable age for enteric fever and its complications is 5-10 years. To combat these issues, large-scale vaccination remains a promising option at least in the most susceptible age group (Iftikhar et al., 2018).

RATIONALE:

The purpose of this study is to critically evaluate the superior clinical outcomes provided by combination drug therapy with meropenem and azithromycin or with meropenem monotherapy. With the increasing prevalence of this difficult to manage XDR typhoid fever, identifying the most effective therapeutic strategy has become necessary. There is limited data available which evaluate clinically meaningful outcomes such as time to defervescence, which directly influence duration of hospital stay, healthcare costs and antibiotic exposure. This study aims to provide high quality local evidence to guide rational antibiotic use and optimize management strategies for XDR Salmonella Typhi infection in resource limited settings.

Hypothesis:

Null Hypothesis: There is no difference between Single vs. Combination Drug Therapy in Extensively Drug-Resistant Salmonella typhi in terms of time to defervescence

Alternative Hypothesis: The time to defervescence is shorter with Combination drug therapy than with Single drug therapy in Extensively Drug-Resistant Salmonella Typhi.

OBJECTIVE:

- **Primary Objective**
- To compare **clinical response (defervescence time)** between single and combination antibiotic therapy in children with XDR typhoid fever.
- **Secondary Objectives**
- To compare:
    - Duration of hospital stay
    - Complication rates

Operational Definitions:

Extensively Drug-Resistant (XDR) Typhoid Fever:

A case of typhoid fever caused by *Salmonella enterica* serovar Typhi that meets the following criteria:

1. **Clinical:** Fever ≥38°C with supportive symptoms (abdominal discomfort, headache, malaise).
2. **Laboratory Confirmation:** Blood culture positive for *Salmonella Typhi* with antimicrobial susceptibility
3. **Resistance Profile:** Resistant to first-line antibiotics (ampicillin, chloramphenicol, co-trimoxazole), fluoroquinolones, and third-generation cephalosporins.
4. **Exclusion:** Fever due to other causes (malaria, dengue, pneumonia, UTI) is excluded.

Disease Severity Criteria (XDR Typhoid)

Severity will be classified as:

Uncomplicated Typhoid:

- Fever ≥38°C with systemic symptoms and stable vital signs and no organ dysfunction tolerating oral feed and positive blood culture.

Complicated Typhoid:

Presence of one or more:

- Shock
- Altered sensorium
- GI bleeding
- Intestinal perforation

- Severe anemia (Hb <7 g/dL)
- Thrombocytopenia (<50,000/mm^3)
- Hepatic dysfunction (ALT >3× normal)
- Inability to tolerate oral therapy/persistent vomiting(HDU/ICU requirement)

Single drug therapy: Single drug therapy will be defined as patients who received carbapenem (meropenem).

Combination drug therapy: Combination drug therapy will be carbapenem plus azithromycin. Patients will receive carbapenem intravenously (IV) at a dose of 30mg/kg/dose every 8 hours(maximum 2g per dose) three times a day and azithromycin (oral) at 20 mg/kg/day according to the hospital protocol.

OUTCOME

Defervescence: It will be defined as the return of oral temperature from documented fever to less than 37.5C (99.5F) for more than 48 hours.

Time to defervescence: It will be calculated in days from the point of start of appropriate antimicrobial therapy until defervescence is reached.

Other outcomes, i.e., duration of hospital stay, will also be noted.

Materials & Methods:

Study Design:

Open-label Randomized controlled trial.

Study Setting:

The study will be conducted in the Pediatric Medicine Department, Children's Hospital and Institute of Child Health, Lahore.

Study Duration:

Twelve months after the approval of the synopsis.

Sampling Technique for enrolment:

All eligible patients will be enrolled consecutively.

Randomization: Simple random sampling

Randomization Procedure:

Eligible patients will be randomized 1:1 to receive either meropenem monotherapy or meropenem plus azithromycin, using computer-generated simple randomization at baseline. Disease severity (uncomplicated vs. complicated XDR typhoid) will be recorded at enrollment, and **pre-planned subgroup analyses** will assess whether outcomes differ by severity. This will ensure unbiased allocation while allowing evaluation of treatment effects across clinical subgroups.

Trial Registration:

The study will follow CONSORT guidelines and will be registered at ClinicalTrials.gov prior to patient recruitment.

Sample Size:

"Sample size was calculated using WHO sample size calculator for comparison of two means using data from Ishaque et al."

$$n = \frac{2\sigma^2 (z_{1-\alpha/2} + z_{1-\beta})^2}{(\mu_1 - \mu_2)^2}$$

a. Level of significance = 5%

b. Power of test = 80%

c. Population SD = 2.73

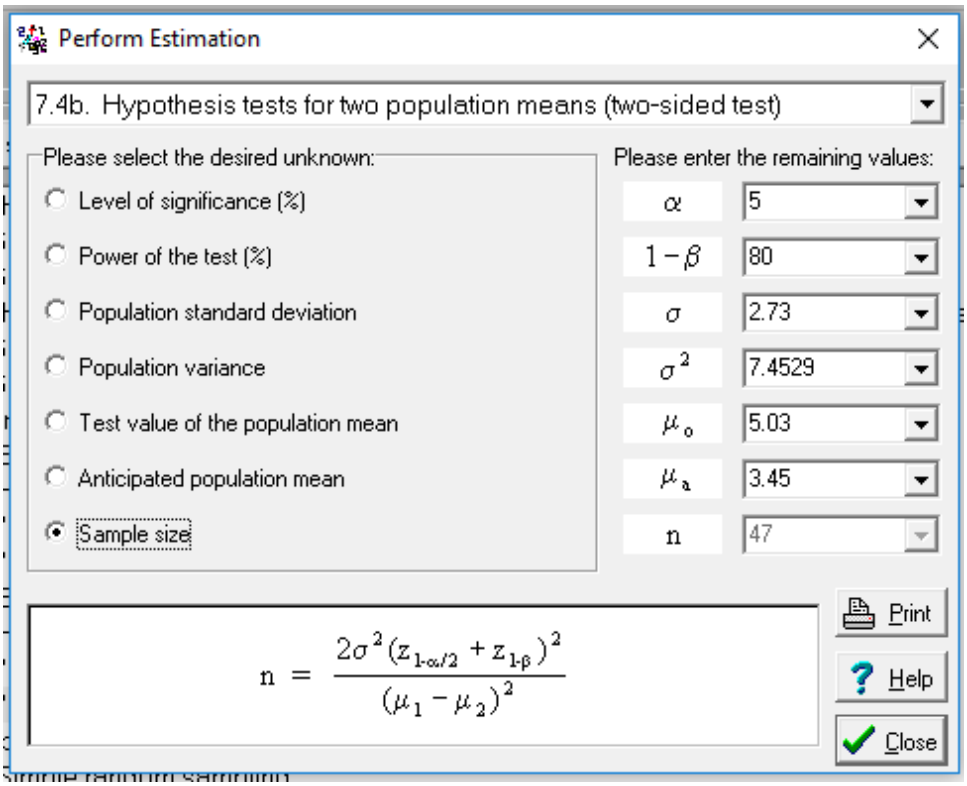
d. Population variance = 7.4529

e. Test value of population mean = 5.03 **(Ishaque et al., 2022**)

f. Anticipated population mean = 3.45 **(Ishaque et al., 2022)**

g. Sample size (n) = 47 patients in each group.

h. Total number of patients = 94.



Sample Selection:

Inclusion Criteria:

- Patients aged between 2 to 16 years.
- Patients of both genders.
- All patients presenting with signs and symptoms of Typhoid fever with positive blood cultures for Salmonella typhi (as per operational definition) admitted in medical wards, notified by the microbiology department as soon as they get a positive culture.

Exclusion Criteria:

- Patients having comorbidities (chronic kidney disease, chronic liver disease, immunodeficiency etc.)
- Patients with any co-infection (malaria, dengue, etc.)
- Patients who refused to participate in the study.
- Patients with incomplete records, especially missing information, duration of treatment, treatment failure, and time to defervescence, will be excluded from the study.

Methodology:

After obtaining approval from the ethical committee of the hospital, a total of 94 patients (47 in each group) presenting in the Department of Pediatric Medicine and meeting the specified selection criteria will be recruited for participation in this study. Comprehensive written informed consent and detailed medical history will be obtained from the legal guardians of all patients. Subsequently, the patients will be randomly allocated into two distinct treatment cohorts:

Group A receiving single drug therapy

Group B receiving combination drug therapy.

Single drug therapy will consist of patients receiving Meropenem will be administered intravenously at a dose of 30 mg/kg/dose every 8 hours(maximum 2g per dose) as per hospital protocol while combination drug therapy will consist of carbapenem (IV) plus azithromycin (orally) at 20 mg/kg/day as per hospital protocol.

Standard Supportive Management during hospitalization/observation:

All patients will receive standardized supportive treatment including:

Antipyretics (Paracetamol 10–15 mg/kg/dose)

- Hydration management
- Electrolyte correction
- Nutritional support
- Monitoring of complications
- Empirical antibiotics (IV Ceftriaxone at dose of 75mg/kg/day in two divided doses)as per hospital policy may be administered until culture and sensitivity results are available. After confirmation of XDR Salmonella Typhi drugs mentioned in study will be initiated according to allocation. Complications will be managed as per hospital protocol and Blood counts will be repeated if clinically indicated.

The process of defervescence and the duration to achieve defervescence will be meticulously documented using a clearly defined operational framework. The primary endpoint of this study will be the **time to defervescence**, with the secondary endpoint being the **length of hospitalization**. All relevant data will be collected using a pre-designed data collection form.

Duration of treatment: Duration of therapy will be 10–14 days for meropenem and 7–10 days for azithromycin, adjusted according to clinical response and complications."

Statistical Analysis:

All data will be entered and analyzed using **SPSS v25.0**.

- **Qualitative data** (e.g., gender, defervescence, complications) will be presented as **frequencies and percentages**.
- **Quantitative data** (e.g., age, duration of fever, hospital stay, time to defervescence) will be presented as **median and interquartile range (IQR)** instead of mean and standard deviation.
- Data normality will be assessed using Shapiro-Wilk test

Statistical tests:

- If normally distributed then Independent sample t-test and if non-normal Mann-Whitney U test will be used to compare **time to defervescence** and **length of hospital stay** between the two treatment groups.
- The **Chi-square test** or **Fisher's exact test** (if expected counts are <5) will be used to compare **defervescence rates** and **complications** between groups.
- A **p-value ≤0.05** will be considered statistically significant.

Outcome &Utilization:

This study aims to compare the treatment outcome between those who will receive single drug therapy (meropenem) versus combination drug therapy (azithromycin plus meropenem). To the best of our knowledge, this is the first study from the local population where we will compare single versus combination drug therapy. Our objective is to contribute to the existing guidelines on the management of this emerging and difficult to treat infection.

Limitations of the study:

It is a single-centered study and will reflect the results of a single center.

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PLAN OF WORK:

Activity	**Months**											
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*
Synopsis and planning of data collection	✓	✓										
Sample collection			✓	✓	✓	✓						
Data entry				✓	✓	✓	✓					
Data analysis							✓	✓				
Thesis writing								✓	✓	✓	✓	✓

Informed Consent Form

Research Participant Consent Form for Research Project,

Children's Hospital and Institute of Child Health, Lahore

Serial no.: _____Date: _____Study center: _____

Name of project: "Comparison of single vs combination drug therapy in extensively drug-resistant Salmonella Typhi in terms of time to defervescence: A randomized controlled trial"

Name of Research Supervisor:	Dr.Sobia Qamar
Designation:	Associate Professor of Pediatrics Medicine Children's Hospital and Institute of Child Health, Lahore.
Name of research in charge:	Dr. Iqra Asghar Ali
Department:	Pediatrics Medicine Department, Children's Hospital and Institute of Child Health, Lahore.
Contact No.:	0306-0942498

Purpose: To compare the mean time to defervescence between Single vs. Combination Drug Therapy in Extensively Drug-Resistant Salmonella typhi

Procedure: Every patient will be informed of the study's purpose and asked to give consent for participation.

Time: 10 to 15 minutes will be required for every participant to participate in this study.

Possible Benefits: All the tests of patients who participated in this study will be guided for treatment.

Financial Consideration: There will be no financial burden on the patient. The financial benefits gained will be free of cost testing for the participant.

Confidentiality: All the records will be confidential, and identities will be treated confidentially. The result of the study will be published for scientific purposes.

Termination from Participation: Every patient will have all the rights to getting excluded from the study even if the consent form is signed.

Authorization:

- I, _____S/o or D/o_____

ID No_____ hereby fully agree to contribute to the above-mentioned study and future related studies on these samples. I was given ample time to think and discuss the study. I understand that this study is designed to add to medical knowledge. I have been informed about the nature of the procedure and the possible risks (s) / discomforts (s) involved. I had the opportunity to ask any questions about the study, and I agree to give _____ samples as requested by _____, the researcher.

- I have also been informed about my explicit right to withdraw from the study at any time if I want to.
- I have no objection in case the data obtained from me, and my investigations(s) are published in a research journal, maintaining confidentiality.
- I have also been informed that my participation / non-participation will not affect my treatment (if applicable).

Patient/ Volunteer/ Subject Name: **Signature**

(Parent/Guardian/Legal Heir in case of Minor / Mental handicap / Deceased)

Researcher Name:

تحقیقی شرکاء کی رضامندی فارم

بچوں کا ہسپتال اور انسٹیٹیوٹ آف چائلڈ ہیلتھ، لاہور

سیریل نمبر: _____

تاریخ: _____

مطالعہ کا مرکز: _____

□ منصوبے کا نام

"انتہائی دوا مزاحم سالمونیلا ٹائفی میں بخار ختم ہونے کے وقت کے لحاظ سے سنگل اور کمبینیشن ادویات کا موازنہ: ایک رینڈمائزڈ کنٹرول ٹرائل"

□□ نگران محقق

ڈاکٹر صوبیہ قمر

اسسٹنٹ پروفیسر، شعبہ اطفال

بچوں کا ہسپتال و انسٹیٹیوٹ آف چائلڈ ہیلتھ، لاہور

□□ تحقیق کی ذمہ دار

ڈاکٹر اقرا اصغر علی

شعبہ: پیڈیاٹرک میڈیسن

بچوں کا ہسپتال و انسٹیٹیوٹ آف چائلڈ ہیلتھ، لاہور

رابطہ نمبر: 0306-0942498

□ مقصد

سنگل اور کمبینیشن دوا تھراپی کے درمیان بخار ختم ہونے کے اوسط وقت کا موازنہ کرنا، ایسے مریضوں میں جنہیں انتہائی دوا مزاحم سالمونیلا ٹائفی ہو۔

□ طریقہ کار

ہر مریض کو تحقیق کے مقصد کے بارے میں بتایا جائے گا اور اس سے شرکت کے لیے رضامندی لی جائے گی۔

□ وقت

ہر شریک کو اس تحقیق میں شامل ہونے کے لیے تقریباً 10 سے 15 منٹ درکار ہوں گے۔

□ ممکنہ فوائد

اس تحقیق میں شامل مریضوں کے تمام ٹیسٹ علاج کی رہنمائی کے لیے استعمال کیے جائیں گے۔

□ مالی پہلو

مریض پر کوئی مالی بوجھ نہیں ہوگا

تحقیق میں شامل افراد کے ٹیسٹ مفت کیے جائیں گے

□ رازداری

تمام ریکارڈ خفیہ رکھے جائیں گے اور شناخت کو بھی راز میں رکھا جائے گا۔ تحقیق کے نتائج صرف سائنسی مقاصد کے لیے شائع کیے جائیں گے۔

□ شرکت ختم کرنے کا حق

ہر مریض کو مکمل اختیار ہوگا کہ وہ کسی بھی وقت تحقیق سے الگ ہو سکتا ہے، چاہے اس نے رضامندی فارم پر دستخط کیے ہوں۔

□ اجازت (Authorization)

میں، _____ ولد/بنت _____

شناختی نمبر _____

یہ اعلان کرتا/کرتی ہوں کہ میں اس تحقیق اور مستقبل میں اس سے متعلقہ تحقیق میں اپنے نمونوں کے استعمال کے لیے رضامند ہوں۔

مجھے غور و فکر اور مشورہ کرنے کے لیے مکمل وقت دیا گیا۔

میں سمجھتا/سمجھتی ہوں کہ یہ تحقیق طبی علم میں اضافہ کے لیے ہے۔

مجھے طریقہ کار اور ممکنہ خطرات یا تکالیف کے بارے میں آگاہ کیا گیا ہے۔

مجھے سوال پوچھنے کا مکمل موقع دیا گیا اور میں _____ نمونے دینے پر رضامند ہوں۔

مزید تصدیق:

مجھے بتایا گیا ہے کہ میں کسی بھی وقت تحقیق سے دستبردار ہو سکتا/سکتی ہوں۔

مجھے کوئی اعتراض نہیں اگر میری معلومات کو رازداری برقرار رکھتے ہوئے تحقیقی جرنل میں شائع کیا جائے۔

میری شرکت یا عدم شرکت میرے علاج پر اثر انداز نہیں ہوگی۔

□ مریض / رضاکار / شریک کا نام

(بصورتِ نابالغ/ذہنی معذوری/وفات: والدین/سرپرست/قانونی وارث)

دستخط: _____

□□ محقق کا نام

دستخط: _____

Ethical Review Certificate

We undertake that:

We will abide by the declaration of the World Medical Association (WMA) made at Declaration of Helsinki (2013, latest amendment) regarding the ethical principles for medical research entitled **"Comparison of single vs combination drug therapy in extensively drug-resistant Salmonella Typhi in terms of time to defervescence: A randomized controlled trial"**

Involving human subjects such as:

1. The health of patients will be the primary consideration.
2. The procedures shall be explained to the subjects clearly, and informed consent shall be obtained.
3. All procedures shall be kept aseptic and painless.
4. Moral and ethical values of no one will be violated during the research.
5. There will be no discrimination based on gender, religion, race or physical orientation.
6. The confidentiality of the information shall be assured and maintained.
7. Data shall be used for publication only.

Dr. Iqra Asghar Ali

Student of MD

Pediatric Medicine

The Children's Hospital Lahore.

Dr. Sobia Qamar

Associate Professor

Department of Pediatrics

The Children's Hospital Lahore.

ACCEPTANCE OF RESPONSIBILITY CERTIFICATE
BY RESEARCH SUPERVISORS AND CO-SUPERVISORS

I hereby undertake:

i. That the synopsis is being submitted by the student Dr.Iqra Asghar Ali So/Do Asghar Ali Registration.No.2015-DGMC-0096-UHS Session 2023 TO 2027Discipline MD PEDIATRICS MEDICINE in line with the prescribed timeline by UHS, and the research project will be completed with submission of thesis within the prescribed time limit;

ii. That any research paper resulting from the research project shall be published, mentioning the affiliation of the author/s with UHS;

iii. That the proposed synopsis is based on original and novel research;

iv. That the research protocol fulfills all ethical obligations prescribed for the conduct of research on human subjects, tissues, biological samples, and experimental animals;

v. That the prescribed format of UHS for synopsis writing, available on its website, has been followed in the manuscript;

vi. To assume full responsibility of the contents of the synopsis and incorporation of any subsequent observations of review committees and Advanced Studies & Research Board, in their true letter and spirit;

vii. That any experiments/techniques mentioned in the synopsis that would be carried outside UHS through collaborative research shall be done after fulfilling all documentary and regulatory requirements as prescribed by the university.

NAME OF SUPERVISOR
Dr. Sobia Qamar
Designation
Associate Professor
Department
Pediatrics medicine
Institution:University of Child Health Sciences &The Children's Hospital Lahore
Date

NAME OF CO-SUPERVISOR:
Dr.Naima Mehdi
Designation:Assistant Professor
Department:Pediatric Microbiology
Institution: University of Child Health Sciences &The Children's Hospital Lahore Date:

PERFORMA

"Comparison of single vs combination drug therapy in extensively drug-resistant Salmonella Typhi in terms of time to defervescence: A randomized controlled trial"

SECTION A: PATIENT IDENTIFICATION

Variable	**Entry**

Study ID :---------- Hospital MR No:---------- Date of Enrolment:------/-------/------

SECTION B: DEMOGRAPHIC INFORMATION

Name	----------	Age(years): ----------
Gender	☐ Male ☐ Female	Weight(kg) :---------
Address	----------	
Socioeconomic Status	☐ Low ☐ Middle ☐ High	

SECTION C: CLINICAL HISTORY

Variable	**Entry**
Duration of Fever (days)	_____
Maximum recorded temperature	_____ °C
History of prior antibiotic use	☐ Yes ☐ No
If yes, specify	_____
Duration of prior antibiotics	_____
Contact with typhoid patient	☐ Yes ☐ No
Vaccination status (Typhoid vaccine)	☐ Yes ☐ No

SECTION D: CLINICAL EXAMINATION

Temperature: ------ Pulse rate: -------- Blood pressure: ---------- Resp. rate: ----------

Level of consciousness	☐ Alert ☐ Irritable ☐ Drowsy
Pallor	☐ Present ☐ Absent
Hepatomegaly	☐ Yes ☐ No
Splenomegaly	☐ Yes ☐ No
Abdominal tenderness	☐ Yes ☐ No

SECTION E: DISEASE SEVERITY CRITERIA

Feature	**Present**	**Absent**
Persistent high fever (>39°C)	☐	☐
Severe abdominal pain	☐	☐
Gastrointestinal bleeding	☐	☐
Altered consciousness	☐	☐

Feature	Present	Absent
Shock	☐	☐
Hepatic dysfunction	☐	☐

Severity classification: ☐ Mild ☐ Moderate ☐ Severe

SECTION F: LABORATORY INVESTIGATIONS

Hemoglobin ------- Total leukocyte count: ------ Platelet count: -------

CRP---ALT------AST------- Blood culture: ☐ Positive ☐Negative

SECTION G: CONFIRMATION OF XDR TYPHOID: Resistance to:

Antibiotic	Resistant
Chloramphenicol	☐
Ampicillin	☐
Trimethoprim-sulfamethoxazole	☐
Fluoroquinolones	☐
Third generation cephalosporin	☐

Confirmed as: ☐ XDR Typhoid

SECTION H: PRIMARY OUTCOME

Outcome	Entry
Time to defervescenc(hours)	_____
Day fever subsided	_____

SECTION I: SECONDARY OUTCOMES

Outcome	Yes	No
Treatment failure	☐	☐
Relapse	☐	☐
Complications	☐	☐
Need for change of antibiotics	☐	☐

COMPLICATIONS:

☐ Intestinal bleeding

☐ Intestinal perforation

☐ Shock

☐ Hepatitis

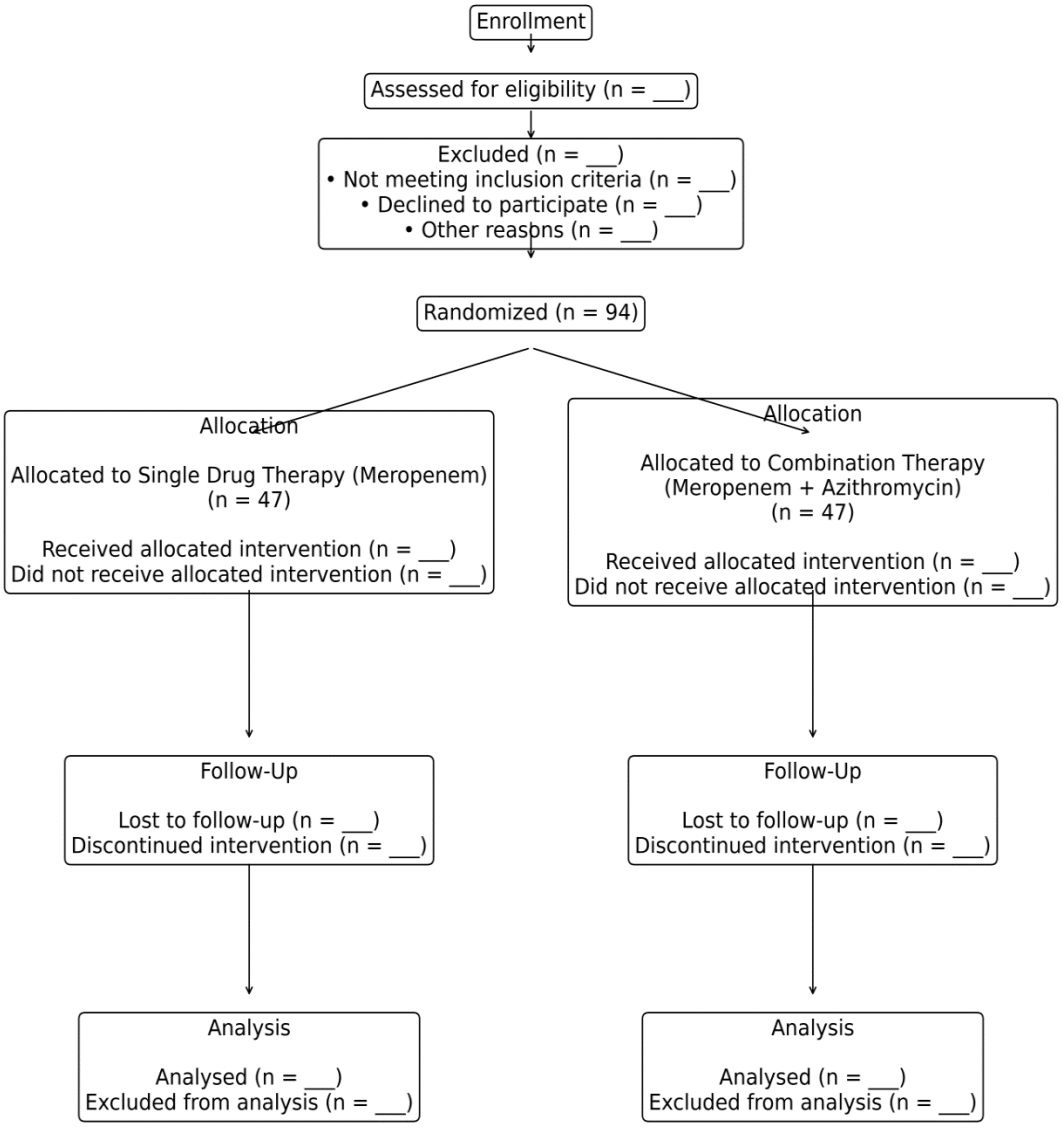
SECTION J: FINAL OUTCOME

Outcome	Entry
Recovered	☐ Yes ☐ No
Length of hospital stay	_____ days

Section/Topic	Item No	Checklist Item	Reported on Page No / Comments
Title and Abstract	1a	Identification as a randomized trial in the title	Title mentions “Randomized Controlled Trial”
	1b	Structured summary of trial design, methods, results, and conclusions	Project Summary, pages iv–1
Introduction	2a	Scientific background and explanation of rationale	Introduction & Literature Review, pages 2–7
	2b	Specific objectives or hypotheses	Objectives & Hypothesis, pages 8–9
Methods	3a	Description of trial design including allocation ratio	Open-label RCT, allocation ratio 1:1, page 11
	3b	Important changes to methods after trial commencement	None reported
	4a	Eligibility criteria for participants	Inclusion/Exclusion criteria, pages 13–14
	4b	Settings and locations where data were collected	Pediatric Medicine Dept., Children’s Hospital & Institute of Child Health, Lahore; page 11
	5	Interventions for each group with sufficient detail	Meropenem IV (20–40 mg/kg/dose every 8 hr), Combination: Meropenem + Azithromycin 20 mg/kg/day oral; pages 14–15
	6a	Completely defined pre-specified primary and secondary outcome measures	Primary: Time to defervescence; Secondary: Hospital stay, complication rates; page 10
	6b	Any changes to trial outcomes after trial commenced	None reported
	7a	How sample size was determined	WHO calculator; SD=2.73, α=5%, power=80%, n=47/group; page 11

	7b	Explanation of interim analyses and stopping guidelines	Not applicable
	8a	Method used to generate random allocation sequence	Computer-generated simple randomization; page 11
	8b	Type of randomization; details of any restriction	Simple randomization, no restrictions; page 11
	9	Mechanism used to implement random allocation	Allocation via computer-generated sequence; patients enrolled consecutively; page 11
	10	Who generated random sequence, enrolled participants, and assigned interventions	Generated and assigned by researcher (Dr. Iqra Asghar Ali); page 11
	11a	Blinding (masking) of participants, care providers, outcome assessors	Open-label; no blinding; page 11
	11b	If relevant, description of similarity of interventions	Not applicable
	12a	Statistical methods for primary and secondary outcomes	Independent t-test / Mann-Whitney U for continuous; Chi-square / Fisher exact for categorical; SPSS v25; page 15
	12b	Methods for additional analyses (e.g., subgroup)	Not planned
Results	13a	Flow of participants (numbers randomized, received intervention, analyzed)	To be reported post-trial
	13b	Losses and exclusions after randomization with reasons	To be reported post-trial
	14a	Dates defining recruitment and follow-up	Study duration: 12 months; page 11
	14b	Why the trial ended or was stopped	N/A
	15	Baseline demographic and clinical characteristics	To be reported in results section
	16	Number of participants analyzed in each group	To be reported post-trial

	17a	For each primary and secondary outcome, results for each group	To be reported post-trial
	17b	Effect size and precision (e.g., 95% CI)	To be reported post-trial
	18	Results of other analyses (e.g., subgroup)	N/A
	19	All important harms or unintended effects	To be reported post-trial
Discussion	20	Trial limitations, addressing sources of potential bias, imprecision	Limitations: single-center, small sample; page 17
	21	Generalizability (external validity) of trial findings	Discussed in Outcome & Utilization; page 16
	22	Interpretation consistent with results, balancing benefits and harms	To be added in discussion chapter
Other Information	23	Registration number and name of trial registry	To be registered on ClinicalTrials.gov; page 11
	24	Where full trial protocol can be accessed	Synopsis available from Department of Pediatrics, Children's Hospital Lahore
	25	Sources of funding and other support; role of funders	Not explicitly mentioned; to be added in annexures


Enrollment
Assessed for eligibility (n = ___)
Excluded (n = ___)
• Not meeting inclusion criteria (n = ___)
• Declined to participate (n = ___)
• Other reasons (n = ___)
Randomized (n = 94)
Allocation
Allocated to Single Drug Therapy (Meropenem)
(n = 47)
Received allocated intervention (n = ___)
Did not receive allocated intervention (n = ___)
Allocation
Allocated to Combination Therapy
(Meropenem + Azithromycin)
(n = 47)
Received allocated intervention (n = ___)
Did not receive allocated intervention (n = ___)
Follow-Up
Lost to follow-up (n = ___)
Discontinued intervention (n = ___)
Follow-Up
Lost to follow-up (n = ___)
Discontinued intervention (n = ___)
Analysis
Analysed (n = ___)
Excluded from analysis (n = ___)
Analysis
Analysed (n = ___)
Excluded from analysis (n = ___)