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

By

Dr. Iqra Asghar Ali

For

MD Pediatrics

under the supervision of

Dr. Sobia Qamar

MBBS, FCPS

Associate Professor of Pediatric Medicine Department

The Children's Hospital, Lahore

University of Child Health Sciences, The Children's Hospital, Lahore

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: Pediatrics Medicine
Name of the Applicant: Dr. Iqra Asghar Ali	D.O.B; 01 November 1995
Nationality: Pakistani	NIC #: 35201-7549690-6
Current Address: 927A Extension State Life Housing Society Lahore. Permanent 927A Extension State Life Housing Society Lahore.	
Phone #: 0306-0942498	E-MAIL: driqraasghar@gmail.com
Qualifications (with passing year): ➢ M.D PEDIATRICS MEDICINE (Continue) ➢ M.B.B.S (2015-2020) ➢ F. Sc. (2014) ➢ Matriculation (2011)	

Practical Experience:

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. (Academic Supervisor)	Signature:	Date:
Prof. Dr. (Head of Department)	Signature:	Date:
Prof. Dr. Masood Sadiq (Vice Chancellor)	Signature:	Date:
Convener, Ethical Review Committee	Signature:	Date:
Chairman (Advanced Studies & Research Board)	Signature:	Date:

☐ Approved ☐ Not Approved

Vice Chancellor, UHS

Contents

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). 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 100 mg/kg/day three times a day 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 will be used 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. (Champney and Burdine, 1998, Champney et al., 1998, Hansen et al., 2002). 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.

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.

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 et al., 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:

This research endeavor is focused on the comparison of treatment outcomes between individuals who are scheduled to undergo either single-drug therapy (meropenem) or combination-drug therapy (azithromycin plus meropenem). It is pertinent to highlight that this particular investigation represents a pioneering effort within the local demographic, as we seek to juxtapose the efficacy of single versus combination drug regimens. Our primary aim is to make a valuable contribution to the existing medical protocols and recommendations concerning the management of this progressively prevalent and challenging-to-treat infection. The study seeks to add novel insights and evidence to the medical community's understanding of optimal treatment strategies for this complex infection, thereby enhancing patient care outcomes and potentially shaping future therapeutic guidelines.

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 true positive for *Salmonella Typhi*.
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.

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 100mg/kg/day 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 100°F 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:

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:

Probability sampling (simple random allocation after eligibility).
All eligible patients presenting during the study period will be recruited consecutively, and then randomly assigned into two treatment groups.

Randomization:

Participants will be randomly allocated into two groups using the lottery method:

- Group A: Single-drug therapy
- Group B: Combination-drug therapy

Allocation will be done using sealed, opaque slips to ensure allocation concealment

Sample Size:

Sample size calculated using the WHO sample size calculator

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

a. Level of significance = 5%

b. Power of test = 80%

c. Population SD = 2.73

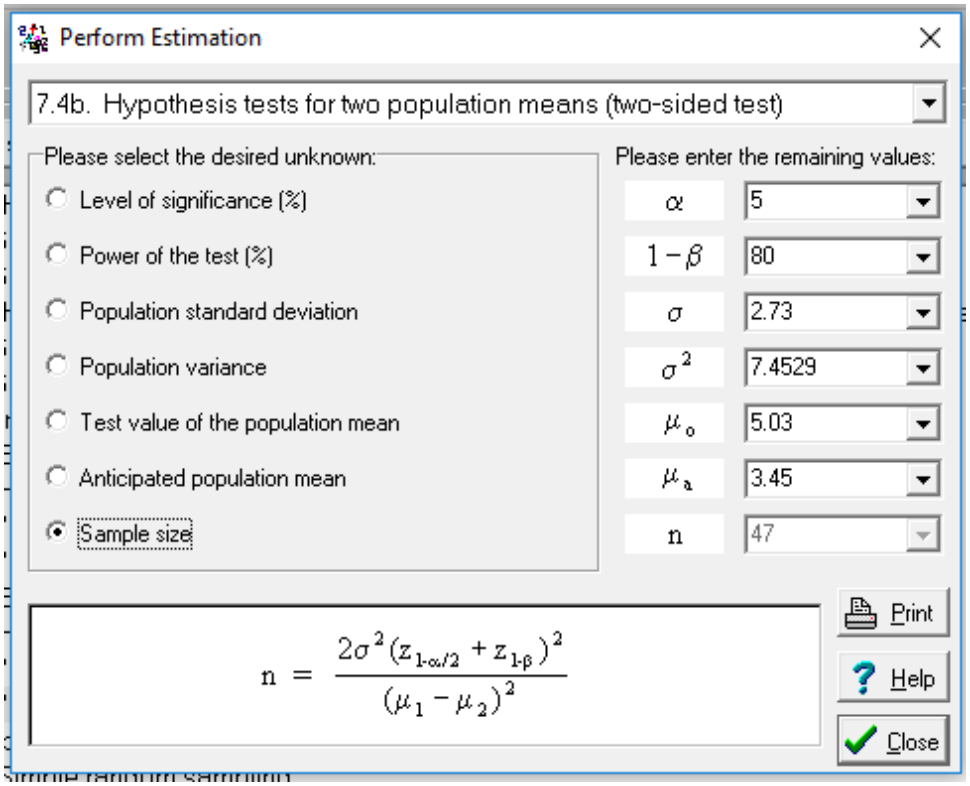
d. Population variance = 7.4529

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 **carbapenem (specifically meropenem)** intravenously at a dose of 100 mg/kg/day thrice daily, while combination drug therapy will consist of **carbapenem (IV) plus azithromycin (orally) at 20 mg/kg/day** as per hospital protocol.

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.

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.

Statistical tests:

- The **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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Annexures: Including:

- **Acceptance of Responsibility Certificate by Research Supervisors & Co-supervisors** (duly signed by the supervisor & co-supervisor) - Prescribed template has been made available at page 13 of this document.
- **Ethical Considerations** (duly signed by the candidate and the supervisor)
- **Informed Consent Proforma** (English & Urdu Translations) – Prescribed template in English has been made available at pages 14-15 of this document.
- **Estimated Cost of the Project:** which includes the funds required for all chemicals / reagents, laboratory equipment/ materials or study animals (if any) to be utilized in the research needs. Cost estimates should be given in an itemized, tabulated format, including all direct and indirect costs.
- **Plan of work (Gantt Chart):** Schedule/Phasing (In order to achieve the desired objectives of the study, divide your work plan into different phases in a tabular form)
- **Data collection tool/s** including proforma, questionnaire, survey, etc.

Note: Covering letter from the institution, and Certificate of approval of Ethical Review Committee/Institutional Review Board shall also be placed with annexures, rather than placing at top of the synopsis.

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								✓	✓	✓	✓	✓

Ethical Review Certificate

We undertake that:

We will abide by the declaration of the World Medical Association (WMA) made at Helsinki (2008) 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.

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: **Signature**

Informed Consent (Urdu)

اجازت نامہ

میں اِس تحقیق میں حصہ لینے کیلئے تیار ہوں

مجھے اِس تحقیق کے متعلق تفصیل سے آگاہ کر دیا گیا ہےاور میں نے اِس کو اچھی طرح سے سمجھ لیا ہے۔۔ میں متعلقہ ڈاکٹر سے اس سلسلے میں مکمل تعاون کروں گا۔اگر کسی بھی وقت میں اس تحقیق میں مزید حصہ نہ لینا چاہوں تو میں اس تحقیق کو چھوڑ سکتا ہوں ۔اس صورت میں میرے علاج پر کوئی اثر نہیں پڑے گا۔

مریض/رشتہ دار کا نام:

دستخط مع تاریخ:

گواہ کا نام:

دستخط مع تاریخ:

محقق ڈاکٹر کا نام:

دستخط مع تاریخ:

ACCEPTANCE OF RESPONSIBILITY CERTIFICATE BY RESEARCH SUPERVISORS AND CO-SUPERVISORS

I hereby undertake:

i. That the synopsis is being submitted by the student_____ So/Do_____ Registration. No._____ Session_____ Discipline_____ 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
Designation
Department
Institution
Date

NAME OF CO-SUPERVISOR
Designation
Department
Institution

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"

Case No: _____ Dated: _____

Name: _____ S/D/O: _____

Weight: _____ kg **Gender: Male ☐ Female ☐**

Contact No: _____

Address: _____

☐ **Group A** (Single drug therapy)

☐ **Group B** (Combination drug therapy)

Duration of fever: _____

Outcome:

Defervescence: Yes No

Time to defervescence of fever: _____ (days)

Hospital stays: ____ (days)

COMPLICATIONS

Thrombocytopenia:	Yes	No
Pancytopenia:	Yes	No
Lower GI bleed:	Yes	No
GI perforation:	Yes	No
Altered sensorium:	Yes	No