GOOD CLINICAL PRACTICES FOR **PROTECT** STUDY

Preparing for Implementation, monitoring, audits, and inspections in a multi-center randomized controlled trial

Pakistan Randomized and Observational Trial to Evaluate Coronavirus Treatment (PROTECT)

Hydroxychloroquine, Oseltamivir and Azithromycin for the treatment of COVID-19 infection: A Randomized Controlled Clinical Trial

Urgency to know what is not known

COMMON MISPERCEPTIONS THAT COMPLICATED RESPONSE

- Level of public health preparedness is adequate
- No more than a seasonal flu
- Sensitive to hot and dry weather
- Herd immunity would be beneficial
- Traditional medicine offers cure
- Only elderly are vulnerable

PROTECT in Response to Little Authenticated Knowledge

- Landmark study to evaluate effectiveness of Hydroxychloroquine (HQ) alone and in combinations with Azithromycin and Oseltamivir

- A multicenter, multiarm, adaptive, randomized control drug trial aimed at COVID 19 +ve patients with mild symptoms across 13 sites in Pakistan

- Carried out under national and international protocols

PRIMARY PATIENT OUTOMES

- The laboratory-based primary outcome will be turning test negative for COVID-19 on RT-qPCR

- The clinical primary outcome will be improvement of two points on a seven-category ordinal scale on day 7 of follow-up

Enrollment Criteria

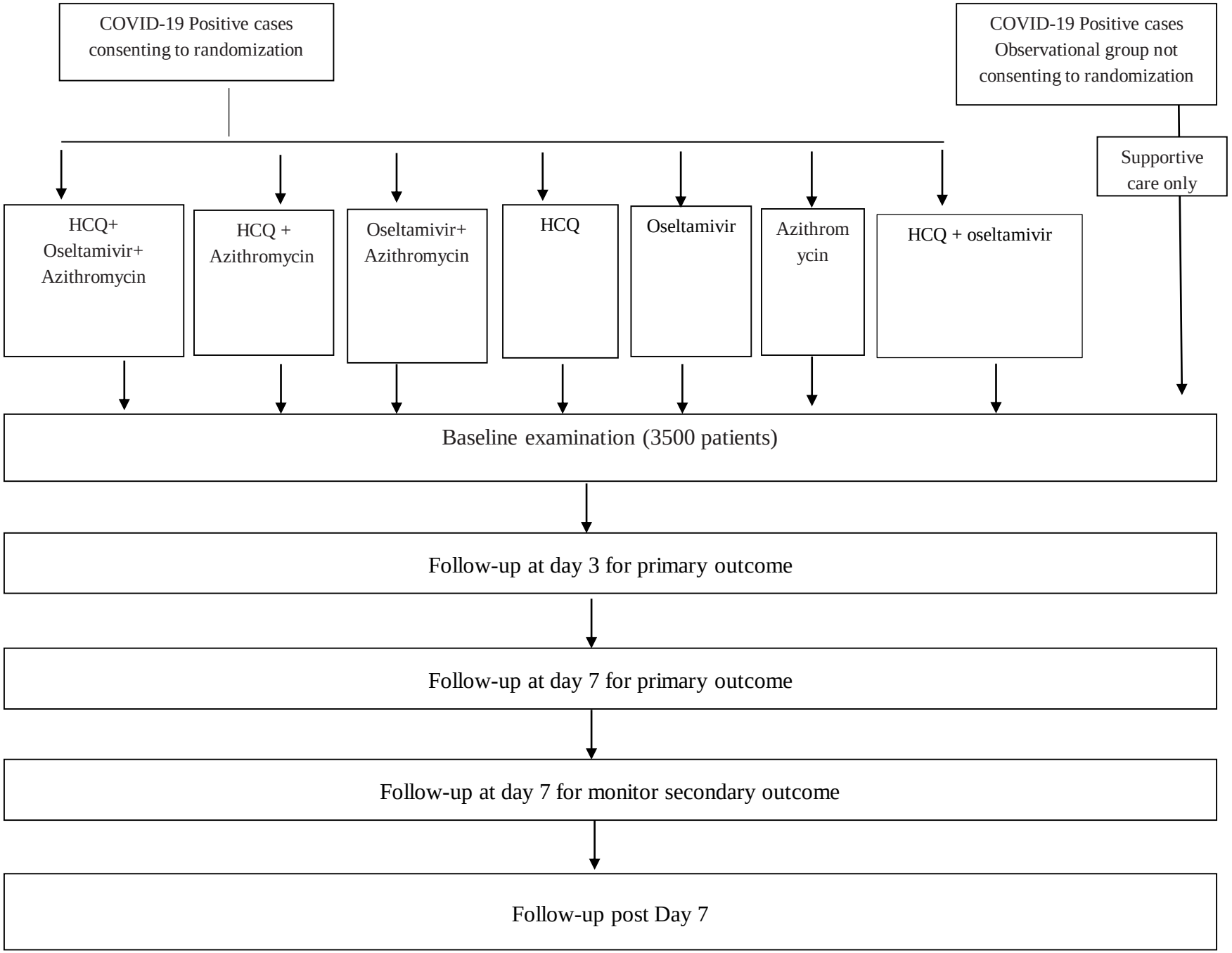
Inclusion Criteria

- Confirmed SARS-CoV-2 (COVID-19) infection by a positive test result
- Either gender
- Symptomatic for example fever, dry cough, slight difficulty to breathe

Exclusion Criteria

- Confirmed absence of SARS-CoV-2 (COVID-19) infection by a negative test result
- Have chronic conditions such as heart disease, liver and kidney failure
- Pregnant or currently lactating
- Immunocompromise and/or systemic disease(s)
- On other antiviral drugs
- History of allergy to any of the drugs to be administered in this study

FLOW CHART OF PROTECT LAYOUT BY GROUPS



Good Clinical Practices (GCP) are defined by ICH as an international ethical and scientific “standard for the design, conduct, performance, monitoring, recording auditing, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate and that rights integrity and confidentiality of the trial subjects are protected”

Investigator *means an individual who actually conducts a clinical investigation at a site. The* ***investigator*** *is the individual who is responsible for administering or dispensing the investigational product to the subject(s), and managing its use in the investigation. If an investigation is conducted by a team of individuals, the investigator is the responsible leader*

WHY GCP IS NEEDED?

- Historic tragedies for example
- The **thalidomide disaster** is one of the darkest episodes in pharmaceutical research history. The drug was marketed as a mild sleeping pill safe even for pregnant women. However, it caused thousands of babies worldwide to be born with malformed limbs. The damage was revealed in 1962 leading to the ban of thalidomide in most countries
- Syphilis experiments of 20th century in which subjects were misinformed and misled

GCP ensures
1- Compliance with vetted treatment protocol
2- Safety and protection of subjects rights
3- Regulatory compliance

The primary objective is to ensure auditable compliance with quality standards at each component of the protocol (Version 1.7)

STEP 1: Organizing Site Teams

STEP 1→ Essential Functions: Medicine Supply Management

- Understand PROTECT protocol
- Prepare demand of medicines, Pre-designate Storage
- Reach out to source of supplies (Mr. Ahmad Butt at UHS)
- Coordinate and receive supplies, keep log
- Dispense supplies to investigator as advised by Team Lead
- Observe stocks and maintain used packaging by date
- Reach out to supplier as needed
- Regularly consult Team Leader for every step

STEP 1→ Essential Functions: Data Management

- Understand PROTECT protocol particularly the CRF
- Requires basic knowledge of ICT, needs a computer and tab with Wi-fi
- Designate Data Center in compliance with disinfection protocols
- Acquire login to IT Dashboard, understand Terms of Use
- Enter baseline data of confirmed cases and on subsequent days as per protocol (IP 111.68.105.8)
- A tab with direct computer input is preferred, use paper if needed. Contact through Team Leader in case of an issue

STEP 1→ Essential Functions: Quality Management

- Means the degree of compliance with protocol
- Supports Team Leader in regular coordination and communication besides maintaining a record of proceedings
- Monitors Adverse Events (AEs) and ensures their reporting on IT Dashboard or paper CRF
- Prompt reporting for troubleshooting or clarification to and via Team Leader
- Maintains a Master File for PROTECT record such as patients' informed consents, team proceedings, AEs' logs, circumstances justifying deviation from protocol

STEP 1→ Essential Functions: External Coordination

- Interacts with team at UHS and trial sites on behalf of Team Leader
- Announces milestones and sentinel events
- Ensure availability or that of surrogate
- Maintains record of all external communication
- Coordinate site-monitoring visits and audits
- Respond to any regulatory queries in consultation with investigators

STEP 1→ Essential Functions: Team Lead

- Identify and delegate essential functions among members
- Ensure continuity of study implementation
- Monitor the process
- Facilitate in case of ambiguities and unforeseen situations
- Ensure broader compliance with study protocol
- Closely observes patient safety aspects and AEs

STEP 2→ Recruitment

COVID +ve (Confirmed)

Informed Consent (added to patient file)

Randomization (Unique ID & allocation to Rx group)

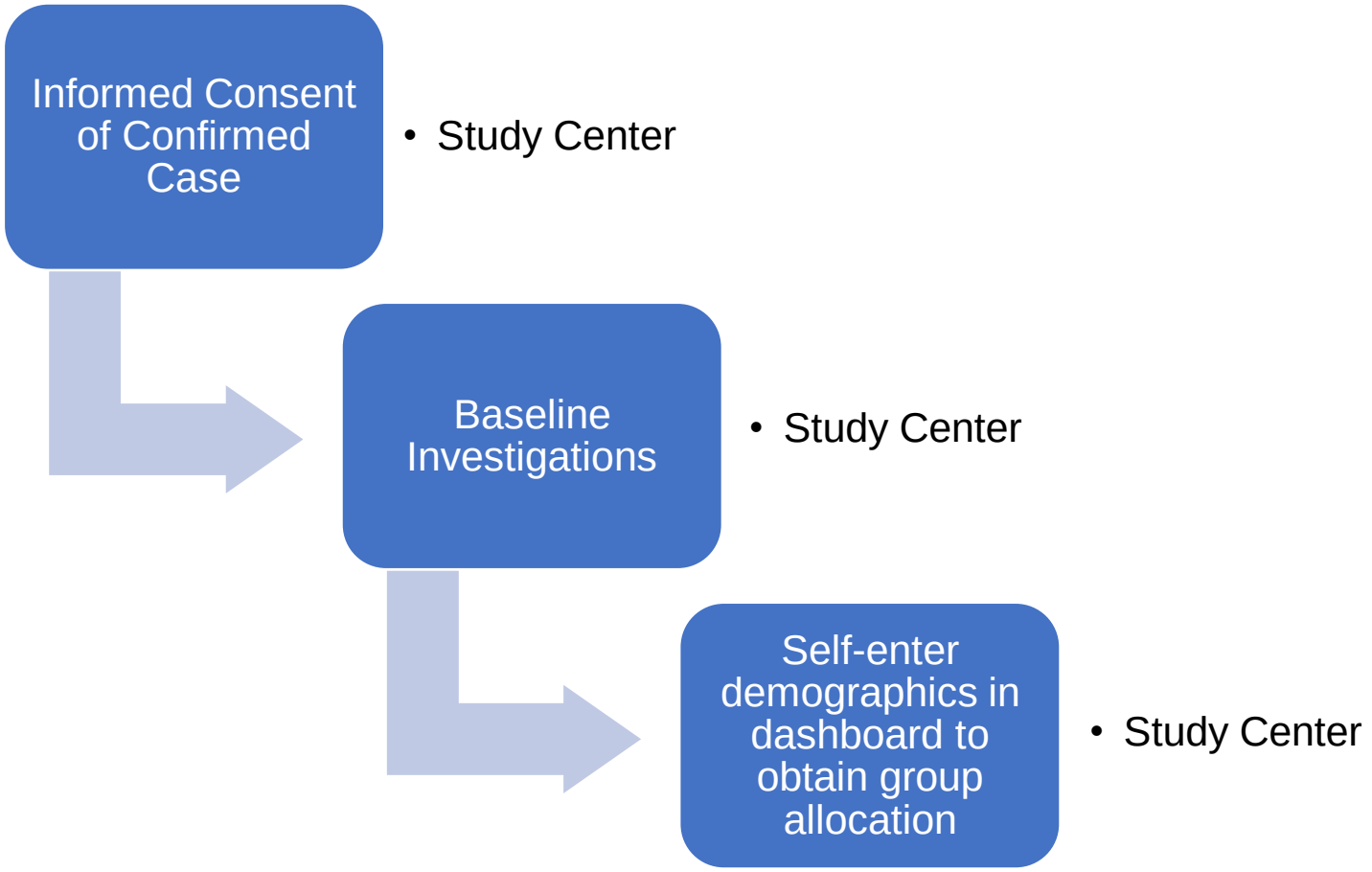
STEP 2→ Informed Consent

- Mandatory and must be maintained
- Study objectives clearly mentioned with risk(s) and benefit(s) explained in plain language
- Written consent form in easy to understand language(s) for those who can write, fields for patient's details and signatures
- Alternative approaches for informing patients who could not read or unable to understand independently
- Approval of consent form by relevant ERC/IRB

STEP 2→ Randomization

- To mimic distribution of characteristics in nature
- Lends highest level of credibility to research
- Quality of RCT is judged by **pharmaceutical audits, a valid informed consent, and credible randomization**
- In this study, sites are responsible for pharmaceutical audits and valid informed consent

HOW TO RANDOMIZE IN THIS CASE



STEP 3→ Data Collection & Entries

Pre-requisites

- A data entry Dashboard has been established at UHS
- Directly write URL in browser address bar
- Exclusive access to designated Site Data Manager
- Accept terms & conditions of data use
- Requires a designated computer with reliable WIFI and disinfection protocol

STEP 3→ Caveats

- Deliberate on modalities of data collection
- **Enter demographics to get group allocation or call biostatistician**
- Direct entries from bedside or other clinical areas would require a WIFI connected tablet
- If patient files and data are disallowed to be brought outside the isolation area, a snapshot of data tools (duly filled) could be taken to a designated desktop/laptop computer setup separate outside (disinfection protocols apply)

Why Quality of RCT matters?

- At top of the research pyramid
- A gold standard
- Any mistake could be seriously consequential
- Challenging methodology
- Requires meticulous planning, execution, and supervision
- Unique challenges in resource-deficient settings

Commonly known factors for success and failures

- Lack of coordination in multicenter settings
- Limited precedent
- Misunderstood methodology and rationale
- Indifference to quality issues such as **pharmaceutical management, informed consent, and randomization**
- Lack of preparation for audits and inspections
- Authorship concerns and competing interests

Monitoring, Audits, Inspections

Monitoring	• Clinical oversight and administrative efforts that monitor a participant's health and efficacy of the treatment during RCT • Sponsor monitors for overall compliance with protocol or justifiable modifications	Clinical monitoring responsibility of site Leads Sponsor responsible for initial and periodic site visits, centralized monitoring, and timely caution
Audits	• RCT audit ensures protection of enrolled subjects • Increases confidence that the data collected and subsequently submitted is valid • Verifies compliance with regulations such as principles of GCPs and tools used for it	Responsibility of third party or Sponsor to visit and submit report
Inspection	• Inspection ensures RCT aligns GCP standards with local regulatory compliance • Interested in framework developed for safety and integrity of subjects and good data quality • Notices any violations and corrective actions	Responsibility of Regulatory authority to visit and submit report

Preparing for Site audits and Inspections

- Keep a Master Site File with roles of team members defined
- Separate folder for enrolled patients' consent on approved form
- Pharmaceutical supply and utilization log, directly observe dose
- Keep proceedings of all internal and external communication
- Prepare evidence of Adverse Events (AEs) monitoring and response
- Evidence of attended GCP training
- Compliance with data management procedures and authenticity

End of Day 3

- Share feedback at shehnoor.azhar@gmail.com
- Practice clinical monitoring and tool sequence and data entries
- Read CRF in PROTECT 1.7