HUMAN RESEARCH ETHICS COMMITTEE: (MEDICAL)

STANDARD OPERATING PROCEDURE

AMENDMENTS

SOP-HREC – 006*(VERSION 1)* **REVISED AND UPDATED: JANUARY 2025**

SUBJECT:	**Procedure for the approval of Amendments to Protocols, Participant Information Leaflets and Informed Consent Forms, Assent Forms, Additional Investigators and Research Entities/Departments, by the University of the Witwatersrand, Human Research Ethics Committee: (Medial)**
DIVISION / SCOPE:	**University of the Witwatersrand, Human Research Ethics Committee (Medical)**
AUTHOR: **REVISION:**	Ethics Secretariat
PURPOSE:	This procedure describes the process to be followed by the Wits HREC (Medical) for the review and approval of Amendments to Protocols, Participant Information Leaflets and Informed Consent Forms, Assent Forms, Additional Investigators and Research Entities/Departments at Wits Affiliated Research Entities/Departments, and Private Practice/External Sites, to ensure that the approvals granted by the Wits HREC (Medical) are in compliance with the following requirements: ♦ South African Good Clinical Practice: Clinical Trial Guidelines. Third Edition (SA GCP 2020) ♦ ICH Harmonised Guideline – Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2) – Current Step 4 version dated 9 November 2016 ♦ South African Ethics in Health Research Guidelines: Principles, Processes and Structures, 2024, 3rd Edition (NDoH 2024) ♦ The applicable FDA requirements for Institutional Review Boards (21 CFR Part 56)
PREVIOUS VERSIONS / ***(REASON FOR REVISION)***	SOP-IEC-002v13 - Previous single SOP split into separate SOPs
CONTENTS:	1. Procedure for review and approval of Amendments by Wits HREC (Medical) 1.1. Amendment Classifications: Minor, Major, Substantive 1.2. Handling Amendments that require only Chair/Co-Chair review 1.3. Handling Amendments that require review from Reviewers 2. Procedure for review and approval for Private Site Applications/External Sites/Investigators 3. Attachments: • Application Form for Amendments to Approved Studies 4. Definitions and Abbreviations 5. References
APPROVALS:	**Signature of Chair / Co-Chair of Wits HREC (Medical)** Paul Ruff **Date:** 2025/01/13

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1. PROCEDURE FOR REVIEW AND APPROVAL OF AMENDMENTS BY THE WITS HREC (MEDICAL)

1.1. AMENDMENT CLASSIFICATIONS

MINOR AMENDMENTS
Changes that do not affect safety, design, analysis/results and are usually administrative in nature. Examples of minor amendments are listed below and are not limited to the following:

a) Additional Site(s)
b) Additional Investigator(s)
c) Change of Investigator(s)/Site Location
d) Change in CRO, Sponsor, Applicant or change of address
e) Increase / decrease in number of local participants
f) Any other administrative changes
g) Changes in the background information – Protocol
h) Extension / redaction of period of study (e.g. low or high recruitment)

MAJOR AMENDMENTS
Changes that affect safety, enrolment, design, analysis/results. Examples of major amendments are listed below and are not limited to the following:

a) Change in inclusion/exclusion criteria
b) Change in objectives of study
c) Change in phase of study
d) Change in study design by removal of study arm
e) Change in: dose of IP (including adjustments), route of administration, change in formulation, manufacturer, frequency, excipients, storage conditions, changes in the manufacturing process and/or specifications of an active substance /IP etc
f) Changes due to new safety data (substantive changes may warrant study termination and subsequent submission of new trial)
g) Any change that impacts on patient safety, quality or the analysis of data (major safety warning may require a new application (e.g study procedures, reducing/increasing number of monitoring visits etc.)
h) Addition of sub-studies
i) Additional tests on stored biological specimens (research based on previously approved study)

SUBSTANTIVE AMENDMENTS REQUIRING NEW CLINICAL TRIAL APPLICATION
The changes that require new application. Examples of changes that require a new trial application are listed below and are not limited to the following:
a) Change in IP
b) Change in standard of care arm
c) Addition of study arm – including comparator or active control arm (except approved as part of initial study)
d) Critical safety warning/s
e) Substantive change in objectives, endpoints and rationale of the study
f) Change in study design with significant impact on statistical analysis or the risk/benefit assessment

1.2. HANDLING MINOR AMENDMENTS THAT REQUIRE ONLY THE CHAIR/CO-CHAIR'S APPROVAL

Responsible:		Action to be taken
Ethics Secretariat	1.	Prepare a Conditional *Amendment Approval Letter* on the Wits HREC (Medical) letterhead for signature by Chair/Co-Chair.
	2.	Forward documents prepared to the Chair/Co-Chair (as applicable): a) Short Cover letter b) Application Form for Amendment to Approved Study c) Summary of changes to the Protocol d) Tracked Changes to the Protocol e) Revised Participant Information Leaflet and Informed Consent form (PIL/ICON), and/or Assent Forms f) Revised Investigator documents: CV, Declaration Form, SA GCP Certificate, Ethics Training Certificate g) Active updated Insurance Certificate (increase in number of participants, extension of study) h) SAHPRA Approval letter of copy of letter submitted to SAHPRA i) Any additional information
	3.	Email **the *Conditional Amendment Approval Letter*** signed by the Chair/Co-Chair to the Sponsor/Applicant and/or Site/Principal Investigator. This document may be sent with a request for a copy of the approval / notification to the SAHPRA for record purposes.
	4.	Save the ***Amendment, supporting documents*** **and** ***Amendment Approval Letter*** on the database.
	5.	Enter the Amendment's approved status into the database.
	6.	Include description of amendment in minutes/agenda of next meeting to ensure that all Wits HREC members are aware of the Chair/Co-Chair's approval of the amendment. (Report generated from database in Amendment section).

1.3 HANDLING MAJOR AMENDMENTS THAT REQUIRE FULL HREC (MEDICAL) APPROVAL

Ethics Secretariat	1.	Major Amendments requires full HREC Approval. Forward a copy of the amendment to two (2) Reviewers (preferably initial, otherwise nominated) for review. Comments are to be received from the Reviewers within 7 days, follow-up if required.
	2.	If the Amendment is approved by the Reviewer(s), prepare a Conditional *Amendment Approval Letter* on the Wits HREC (Medical) letterhead for signature by Chair/Co-Chair.

3. Forward documents prepared to the Chair/Co-Chair

4. Email **the *Conditional Amendment Approval Letter*** signed by the Chair/Co-Chair to the Sponsor/Applicant and/or Site/Principal Investigator. This document may be sent with a request for a copy of the approval / notification to the SAHPRA for record purposes.

5. Save the ***Amendment, supporting documents*** **and** ***Amendment Approval Letter*** on the database.

6. Enter the Amendment's approved status into the database.

7. Include description of amendment in minutes/agenda of next meeting to ensure that all HREC members are aware of the approval of the major amendment. (Report generated from database in Amendment section).

8. If the major amendment is not approved by the Reviewer's, this will be tabled at the Wits HREC (Medical) meeting for further discussion and deliberation.

2. PROCEDURE FOR REVIEW AND APPROVAL FOR PRIVATE SITE APPLICATIONS / EXTERNAL SITES / INVESTIGATORS

2.1 Investigators/Researchers Affiliated With Other Universities In South Africa

The University of the Witwatersrand, Human Research Ethics Committee: (Medical) will no longer be able to review and/or approve applications/studies/projects from Investigators/Researchers affiliated to other Universities in South Africa, **unless they have a joint affiliation with the University of the Witwatersrand.**

Sponsor/Applicants of studies with Investigators/Researchers affiliated to other Universities should submit their applications/proposals to their own University HREC.

Wits HREC (Medical) will however continue to provide ethics support for previously approved studies such as amendments, until the expiry of the existing Wits HREC (Medical) approval. However, addition of new Researchers/Investigators and Sites will become the responsibility of the University concerned.

As the Wits HREC (Medical) has no jurisdiction over Investigators/Researchers affiliated with other South African Universities, other than the University of the Witwatersrand, it is unable to provide oversight and authority over such Investigators/Researchers.

2.2 External/Private Site/Investigator Applications (within Gauteng Province only)

External/Private Sites/Investigators (within Gauteng Province only) may be submitted to the Wits HREC (Medical), however 1) there must be at least one Wits affiliated site involved in the study, and 2) the Memorandum of Agreement (MoA) for External Research Sites (an agreement between the University of the Witwatersrand, the Sponsor/Applicant and the External Site/Principal Investigator) must be completed and submitted with applications.

This MOA will be required for all external/private site applications (new and additional sites added to ongoing studies), going forward.
This MOA will give the Wits HREC (Medical) proper jurisdiction to oversee the external/private sites.

2.3 External/Private Research Sites outside of Gauteng Province

The University of the Witwatersrand, Human Research Ethics Committee: (Medical) will no longer be able to approve External/Private Research Sites outside of the Gauteng Province. This decision is due to increased monitoring pressures and difficulties in oversight.

As per South African Ethics in Health Research Guidelines: Principles, Processes and Structures 2024, Third Edition, Chapter 5, Section 5.5.1.4 a):

"The South African ethico-legal framework requires that PIs or research leaders must obtain approval from their institutional REC. In principle, this means that RECs have authority to review and approve research protocols only for research sites or ***geographic areas within their own South African jurisdiction****. Thus, when a protocol proposes a research study or project that is to collect data from multiple sites or geographic areas within South Africa, more than one REC may be involved in the review and approval processes."*

Therefore External/Private Research sites outside of Gauteng Province should be submitted to HRECs within their own geographical area.

The HREC (Medical) will however continue to provide ethics support for previously approved External/Private Research Sites outside of Gauteng Province, until the expiry of the existing HREC (Medical) approval (either initial approval or recertification).

For now, External/Private Sites due for recertification will be provided with HREC approval for one year only, thereafter the site will have to obtain HREC approval elsewhere, however this will be reviewed on a case by case basis. Recertification will however be given for studies that are planned for closure in the near future.

Please be advised that all external sites affiliated with the University of the Witwatersrand will be considered for approval regardless of their location in South Africa, outside Gauteng Province.

All sites, regardless of their location in South Africa, must have SOPs in place to deal with medical emergencies, including immediate access to functioning resuscitation equipment and urgent hospital admission.

The HREC (Medical) is committed to ensuring that all Wits affiliated sites in South Africa meet the necessary ethical standards and requirements for research approval.

2.4 Foreign Research Sites and Investigators

As Wits HREC (Medical) has no jurisdiction outside the borders of South Africa, it cannot provide ethics approval for any foreign site. This is therefore the responsibility of their local IEC/IRBs based on the legal requirements of the country concerned.

Wits Investigators working at foreign sites will need approval from the Wits HREC (Medical) as well as the applicable IEC/IRBs of the country concerned.

Foreign Investigators working in South African sites affiliated with the University of the Witwatersrand, will require Wits HREC (Medical) approval, as well as that of their own institution.

3. ATTACHMENTS

- Application Form for Amendments to Approved Studies
- HREC Memorandum of Agreement (MoA)

4. DEFINITIONS AND ABBREVIATIONS

CFR	Code of Federal Regulations (USA)
FDA	Food and Drug Administration (USA)
GCP	Good Clinical Practice
ICH	International Council for Harmonisation
HREC	Human Research Ethics Committee
MOA	Memorandum of Agreement
SAGCP	South African Good Clinical Practice: Clinical Trial Guidelines. Third Edition (SA GCP 2020)
WHC	Wits Health Consortium
WITS	University of the Witwatersrand

5. REFERENCES

- South African Good Clinical Practice: Clinical Trial Guidelines. Third Edition (SA GCP 2020)
- ICH Harmonised Guideline – Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH – E6(R2) – Current Step 4 version dated 9 November 2016
- South African Ethics in Health Research Guidelines: Principles, Processes and Structures, 2024, 3rd Edition (NDoH 2024)
- International Ethical Guidelines for Health-related Research Involving Humans, Fourth Edition. Geneva. Council for International Organizations of Medical Sciences (CIOMS); 2016.
- WMA, Declaration of Helsinki 2024
- 21 Code of Federal Regulations Part 56 – Institutional Review Boards
- 21 Code of Federal Regulations part 50 – Protection of Human Participants
- Association of British Pharmaceutical Industries (ABPI 2014)