PROTOCOL MICOR-304-101
VERSION A.6
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A PROSPECTIVE MULTICENTER STUDY TO ASSESS THE CLINICAL OUTCOMES OF LOW ENERGY LENS FRAGMENTATION CATARACT EXTRACTION IN PATIENTS UNDERGOING CATARACT SURGERY

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1 PERSONNEL AND FACILITIES

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2 STUDY SYNOPSIS

Study Objective

The purpose of this research study is to evaluate the clinical outcomes of the use of low-energy segment removal with a micro-interventional irrigation/aspiration port (MICOR-304) to evacuate the lens prior to intraocular lens insertion in subjects undergoing routine cataract surgery.

Study Population

Only 1 eye per subject will be enrolled into the study. Up to 100 subjects (100 eyes) will be enrolled into the first phase of the study and an additional 200 subjects (200 eyes) will be enrolled in the second phase of the study, for a total of 300 subjects (300 eyes). Subjects will be enrolled in one of the two cohorts of this clinical investigation. For the first 100 eyes enrolled – up to 75 eyes may be enrolled in Cohort 1 and up to 75 eyes in Cohort 2. For the additional second phase of 200 eyes – up 150 eyes may be enrolled in Cohort 1 and up to 150 eyes in Cohort 2. Overall, for the 300-study eye investigation, there should be no more than 225 eyes in either Cohort 1 or 2.

Study Design

This is multicenter, multi-cohort, prospective clinical study designed to provide longitudinal, observational, non-comparative clinical outcome data for mechanical non-phacoemulsification lens extraction using low-energy segment removal with a micro-interventional irrigation/aspiration port (MICOR-304) to evacuate the lens prior to intraocular lens insertion.

Subjects will be stratified into two Cohorts. Cohort 1 is comprised of eyes with mild-to-moderate cataracts only (Grade 1 to 2). Cohort 2 is comprised of eyes with moderate to more dense cataracts only (Grade 2+ to 3+).

Inclusion Criteria

1. Able to understand study requirements, willing to follow study instructions and willing to return for required study follow-up visits.
2. Willing and able to understand and complete the informed consent document
3. Subjects with a cataract grade of 1 to 3+ and are scheduled to undergo cataract surgery
4. Subjects $\geq$ 18 years of age

5. Clear intraocular media, other than cataract

Exclusion Criteria for both Cohorts

1. Polar cataracts
2. Zonular instability
3. Subjects who have been diagnosed with dry eye which has been untreated and or would affect postoperative visual acuity outcomes (i.e., if the subject has had dry eye treatments / devices and has, or is undergoing treatment and deemed to be stable, they would be an eligible study candidate).
4. Concurrent participation or participation in any clinical trial up to 30 days prior to preoperative visit.
5. Subjects that are pregnant, lactating or planning to become pregnant during the course of the study

Primary Endpoint

Efficacy: Total lens removal time and amount of irrigation solution fluid volume used during the surgical procedure.

- Total lens removal time is defined in two phases:
    - The beginning time starts when the surgeon enters into the eye with the MICOR-304 to start the lens removal process and completing when the surgeon finishes the nucleus lens removal with the MICOR-304 before changing over to irrigation and aspiration.
    - The second phase of lens removal time is the irrigation and aspiration stage for cortex removal which starts when the irrigation and aspiration tip enters the eye and completion time is when the cortex is removed.
- Total irrigation solution volume will be recorded using the indicators on the waste bag which will have labels that have pre-defined markers to indicate milliliters (ml) of volume of irrigation solution used for the surgical procedure.

Safety: Rate of occurrence of intraoperative and postoperative adverse events (AEs)

Secondary Endpoints

- UCVA on day 1
- BCVA on days 7, 30
- Change in corneal thickness from baseline through Day 30
- Rate of occurrence of intraoperative and postoperative adverse events (AE)
- Results of slit lamp and fundus examinations, which are not considered to be AEs

- Total procedure time: defined as the beginning time when the surgeon makes the first incision in the eye and completion time is when the eye speculum is removed at the end of the procedure.

Schedule of Visits

Screening visit, intraoperative visit, post-operative day 1, day 7, day 30.

3 INTRODUCTION AND RATIONALE

Background

Global estimates suggest that 94 million people are visually impaired due to cataract and, of these, 20 million are blind.[1] Because the incidence of cataracts increases with age, an increase in the elderly population will lead to a significant increase in cataract prevalence. Approximately 25% of people aged 65-69 years have cataracts, a proportion increasing to over 68% of those aged 80+ years.[3]

In 2014, nearly 23 million cataract surgeries were performed worldwide; of these, over 3.6 million procedures were performed each in the US and EU.[4] Cataract extraction with intraocular lens (IOL) implantation is the most commonly performed surgical procedure in the world. The safety and effectiveness outcomes of modern-day cataract surgery are well described in the literature.[6] Technological advances have transformed cataract surgery so that now over 99% are performed on an outpatient basis with excellent surgical outcomes.[8]

As cataract surgery has become minimally invasive and more procedural in nature, it has been performed much earlier in the course of disease and patients' lives. It is not uncommon to perform cataract surgery in the patient's 5th decade rather than their 70's even at very low levels of visual impairment. This early intervention has placed additional emphasis on safety and reduced ocular trauma during cataract surgery.

Current phacoemulsification approach to cataract extraction involves high-frequency thermogenic ultrasonic needle to fragment the lens and remove it from the anterior segment of the eye. This can be associated with significant ocular morbidity particularly in advanced cataracts because the phacoemulsification needle produces significant amount of energy and generates heat which is detrimental to the cornea and the endothelium.

Mechanical approaches to lens fragmentation and aspiration such as the MICOR-304 fragmentation and lens removal provide an alternative to phacoemulsification with no cavitation, no thermogenic energy in the eye which can eliminate the generation of heat inside the eye while at the same time maintaining the same minimally invasive surgical approach through a small clear-cornea 2.5 mm incision.

[redacted]

[redacted]

4 STUDY OBJECTIVES

The purpose of this research study is to characterize the clinical outcomes of mechanical and ultrasound-assisted lens fragmentation techniques in routine cataract surgery. The study will provide longitudinal, observational, non-comparative clinical outcomes data for mechanical lens fragmentation techniques.

5. STUDY DESIGN

This study protocol is a dual cohort, prospective, multi-center, interventional study whose goal is to evaluate the clinical and surgical outcomes of mechanical lens fragmentation techniques. The study is planned for up to 10 investigational sites. Only 1 eye per study subject will be enrolled into the study.

[redacted]

6. STUDY POPULATION

Individuals will be assessed for study eligibility based on the criteria presented below:

Inclusion Criteria

1. Able to understand study requirements, willing to follow study instructions and willing to return for required study follow-up visits
2. Willing and able to understand and complete the informed consent document
3. Subjects with a cataract grade of 1 to 3+ and are scheduled to undergo cataract surgery
4. Subjects ≥ 18 years of age
5. Clear intraocular media, other than cataract

Exclusion Criteria for both Cohorts

1. Polar cataracts
2. Zonular instability
3. Subjects who have been diagnosed with dry eye which has been untreated and or would affect postoperative visual acuity outcomes (i.e., if the subject has had dry eye treatments / devices and has, or is undergoing treatment and deemed to be stable, they would be an eligible study).
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- Total irrigation solution volume will be recorded using the indicators on the waste bag which will have labels that have pre-defined markers to indicate milliliters (ml) of volume of irrigation solution used for the surgical procedure.

Safety: Rate of occurrence of intraoperative and postoperative adverse events (AE)

Secondary Endpoints

- UCVA on day 1,7,30
- Change in corneal thickness from baseline through Day 30
- Rate of occurrence of intraoperative and postoperative adverse events (AE)
- Results of slit lamp and fundus examinations, which are not considered to be AEs
- Total procedure time is defined as the beginning time when the surgeon makes the first incision in the eye and completion time is when the eye speculum is removed at the end of the procedure

Schedule of Visits

Screening visit, intraoperative visit, post-operative day 1, day 7, day 30

7 STUDY PROCEDURES

Subject Entry

Participants who meet the inclusion and exclusion will be asked to enroll in the study. The investigator or designee will explain the study purpose, procedures and responsibilities to the potential participant and provide sufficient opportunity to ask questions, while allowing adequate time for consideration of the information provided. Upon participant confirmation of interest, written informed consent will be obtained and the subject will be enrolled in the study. One copy of the informed consent document (ICD) will be retained with the subject's medical records and one copy will be provided to the subject.

Subject Cohort Selection:

Subjects with mild to moderate cataracts (Grade 1-2) who meet the inclusion criteria, will be assigned to Cohort 1. Subjects with severe cataracts (Grade 2+ - 3+) meeting the inclusion criteria will be assigned to cohort 2. Subjects with intermediate cataracts, which may qualify for either Cohort, will be assigned based on investigator discretion and clinical judgement since exact lens density judgment is impossible to determine prior to surgery.

Only 1 eye per subject will be enrolled into the study. Up to 100 subjects (100 eyes) will be enrolled into the first phase of the study and an additional 200 subjects (200 eyes) will be enrolled in the second phase of the study, for a total of 300 subjects (300 eyes). Subjects will

be enrolled in one of the two cohorts of this clinical investigation. For the first 100 eyes enrolled – up to 75 eyes in Cohort 1 and up to 75 eyes in Cohort 2. For the additional second phase of 200 eyes – up 150 eyes per subject in Cohort 1 and up to 150 eyes in Cohort 2. Overall, for the 300 study eye investigation, there should be no more than 225 eyes in either Cohort 1 or 2.

Surgical Procedure

All subjects will undergo routine cataract surgical intervention with IOL implantation. All subjects will receive the standard of care preoperative and peri-operative medications and assessments. The procedure can be performed under either topical or peri/retrobulbar anesthesia per investigator discretion. Clear cornea cataract surgery will be performed with the following steps:

[redacted]

Study Eye

For each subject, one or both eyes may be treated; however, if both eyes are scheduled for treatment, then one eye will be designated as the “study eye” based on investigator discretion prior to any surgical intervention.

Study Visits

All subjects enrolled will return for defined follow-up visits pre- and post-operatively. Data collected from each scheduled and unscheduled (or interim) exam will be recorded on a Case Report Form (CRF).

Subjects who become ineligible for study participation after enrollment will be exited from the study and the reason for exit will be documented on the Subject Screening Log and noted as a screen failure.

Pre-Operative/Screening Visit

This visit can occur 0 to 60 days prior to surgery. The following information will be captured for the study eye at this visit:

- Demographic data (gender, age, race / ethnicity)
- Ocular history / ocular medications
- Cohort selection 1 or 2
- Identification of study eye (OS or OD)
- Cataract type and grade
- Manifest refraction and best-corrected visual acuity (BCVA)
- Slit lamp biomicroscopy
- Dilated pupil size measurement
- Goldmann tonometry
- Dilated fundus examination and C:D ratio assessment
- Central corneal pachymetry
- Macular OCT (optional)

Intraoperative

The following information will be captured for the study eye during surgery:

- Total lens removal time
- Total volume of irrigation fluid used
- Anesthesia type
- Other surgical procedures performed
- Device failure / malfunction
- Method / device used for cataract pre-segmentation
- MICOR-304 model used
- Type of viscoelastic used
- Total procedure time
- Any intraoperative AEs (capsule tear, corneal haze, other)

1 DAY Postoperative

This visit must occur at postoperative days 1-2. The following information will be captured for the study eye at this visit:

- Ocular medications

- UCVA (pinhole)
- Slit lamp biomicroscopy
- Goldmann tonometry
- Central corneal pachymetry
- AE assessment
- Macular OCT (optional)

1 WEEK Postoperative

This visit must occur at postoperative days 5-10. The following information will be captured for the study eye at this visit:

- Ocular medications
- Manifest BCVA
- Slit lamp biomicroscopy
- Goldmann tonometry
- Central corneal pachymetry
- AE assessment
- Macular OCT (optional)

1 MONTH Postoperative

This visit must occur at postoperative days 21-35. The following information will be captured for the study eye at this visit:

- Ocular medications
- Manifest BCVA
- Slit lamp biomicroscopy
- Goldmann tonometry
- Central corneal pachymetry
- Dilated fundus examination and C:D ratio assessment
- AE assessment
- Macular OCT (optional)

The examinations associated with each study visit are outlined and summarized in **Appendix 1** (Schedule of Events and Procedures) and a description of methodology for these examinations is provided in **Appendix 2** (Examination Procedures, Tests, Equipment and Techniques).

Unscheduled Visits

Unscheduled visits are those which are not required by the study protocol, but which occur due to a surgical procedure performed on the study eye, or a subject complaint regarding this eye. No specific testing is required at unscheduled visits; rather, the Investigator and/or qualified investigational staff will perform the procedures necessary to evaluate the subject at these visits. Clinical data from these visits will be recorded on the relevant CRF.

Subject Identification

The subjects will be identified by a five digit number comprised of a two-digit site number followed by a three-digit subject # (e.g., 01-001, 01-002, 01-003 etc.). The subject identification number will be assigned when informed consent is obtained.

Source Documents and Case Report Forms

Adequate original records will be maintained for the study. All original source documents will be retained at the site. The study sponsor, sponsor's representative, and appropriate regulatory authorities shall have access to the source documents as needed.

8 STATISTICAL METHODS

Analysis Plan

Primary and secondary endpoints will be analyzed with descriptive statistics. Point estimates and confidence intervals will be calculated for each outcome. 95% confidence intervals for lens removal time and irrigation fluid volume will be calculated based on a t distribution.

Frequency tabulations of safety outcomes will be made at the 1 week and 1-month follow-up evaluations.

Sample Size

The sample size for this study is based on the following:
For safety, the pooled sample of 100 eyes will have a greater than 90% chance of detecting one or more rare adverse events, i.e., those with an expected rate of occurrence of 2.5%.
We anticipate that for Cohort 1 (grades 1 – 2) the mean lens removal time will be approximately 5 minutes, with standard deviation of 1 minute, and for Cohort 2 (grades 2+) the mean lens removal time will be about 10 minutes, with standard deviation 2 minutes. Under

these assumptions a sample of 50 eyes will produce a confidence interval width of approximately 0.56 minutes for Cohort 1 and 1.14 minutes for Cohort 2.

For Irrigation Fluid Volume we anticipate a mean of 30ml with a standard deviation of approximately 5ml for both Cohorts. Under these assumptions, a sample of 50 eyes will produce a confidence interval width of approximately 2.8ml for each Cohort.

Adverse Events

The number of subjects reporting at least 1 AE of a given type will be summarized. AEs not listed that occur during the study will be added to the summary of AEs. Summaries will also be provided for AEs considered to be related to the device. Each AE will be summarized by incidence and percentage.

Central Corneal Pachymetry

Central corneal pachymetry data will be summarized with N, mean, standard deviation, minima, median, and maxima. A 95% confidence interval will be provided for the change and percentage change from baseline. Change between two consecutive visits will also be summarized.

Slit Lamp and Fundus Exam Findings

Slit lamp, and fundus examination findings at scheduled follow-up visits will be tabulated such that the number and percentage of subjects in each category will be summarized.

9 ADVERSE EVENTS

All ocular AEs in the study eye must be reported on the relevant CRF. AEs will be categorized by degree of harm to the subject (mild, moderate, or severe).

Ocular conditions or diseases present at the time of study enrollment will be considered as “baseline”. Changes in a chronic condition or disease that are consistent with natural disease progression are not considered AEs.

AEs that might reasonably be expected to occur include, but are not limited to, the following:

- Anterior chamber cell and flare requiring initiation of steroid treatment

- Capsular tear and rupture
- Vitreous loss
- Endophthalmitis
- Corneal edema
- Retinal tear / detachment
- Dialysis, flap tears or proliferative vitreoretinopathy
- Cystoid Macular Edema
- Hypopyon
- Hyphema
- Lens dislocation
- Pupillary block
- Acute corneal decompensation
- Raised IOP requiring treatment
- Severe inflammation
- Secondary Surgical Intervention

Grading of Adverse Events

AEs will be graded on a 3-point scale (mild, moderate, severe) using the following definitions:

- Mild: Discomfort noticed, but there is no disruption of normal daily activity
- Moderate: Discomfort is sufficient to reduce or affect normal daily activity
- Severe: Subject is incapacitated as evidenced by the inability to work or perform normal daily activity

Follow-up of Adverse Events

AEs will be followed until resolution or stabilization of the event.

Expedited Reporting of Adverse Events

An AE should be classified as SERIOUS if it:

- Caused or led to death.
- Was life threatening (i.e., the AE placed the subject at immediate risk of death).
- Required or prolonged inpatient hospitalization (i.e., the AE required at least a 24-hour inpatient hospitalization or prolonged a hospitalization beyond the expected length of stay).
- Was sight threatening.

- Was disabling (i.e., the AE resulted in a substantial disruption of the subject's ability to carry out normal life functions).
- Resulted in a congenital anomaly/birth defect (i.e., an adverse outcome in a child or fetus of a subject due to participation in this study).
- Does not meet any of the above serious criteria but jeopardized the subject by requiring medical or surgical intervention to prevent one of the outcomes listed above.

Serious events or serious device related adverse events should be reported in accordance with the following requirements:

Event Type	Reporting Timeframe
Serious device related adverse event	Within 24 hours of becoming aware of the event
SAE	Within 1 week of becoming aware of the event

Any ocular-related serious adverse event (SAE) should be reported to the study sponsor WITHIN ONE WORKING DAY of learning of the event. Non-ocular-related SAEs should be reported to the study sponsor within TWO WORKING DAYS of learning of the event. Email the Adverse Event CRF to gary@gsmservicesus.com
Any serious device related adverse events must be reported to the following three entities:

1. The study sponsor – Within ONE WORKING DAY of the investigator first learning of the event, email the AE CRF to gary@gsmservicesus.com; and
2. The reviewing Institutional Review Board(IRB) Committee – As soon as possible, but no later than 7 working days after the investigator first learns of the event, report per the IRB instructions.
3. FDA under the reporting requirements for 21 CFR Part 803 Medical Device Reporting

10 ETHICAL AND REGULATORY CONSIDERATIONS

This protocol was designed and will be conducted in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later amendments. Basic responsibilities of the study Investigators and overseeing Institutional Review Board(s) (IRB) are as noted below:

Investigator Responsibilities

The Investigator is responsible for maintaining clinical study records and reports as noted below for at least 2 years following the latter of: the date which the study is terminated or

completed, or the date that the records are no longer required for purposes of supporting a marketing application. The Investigator will make these records available for audit and review by FDA as requested by the Agency.

Clinical Study Records:

- AEs
- Signed Investigator Agreements and Investigator *Curriculum Vitae* (CV)
- Financial disclosure information under 21 CFR Part 54
- Study Electronic Case Report Forms
- Study-related correspondence

Clinical Study Reporting:

- Results of evaluation of any serious device related adverse event to all Investigators, IRBs and FDA in accordance with reporting requirements under 21 CFR Part 803 Medical Device Reporting after receiving notice of the event
- Withdrawal of IRB approval to all Investigators, IRBs and FDA within 5 working days
- Progress reports to all IRBs annually or as required by the IRB
- Final report to all IRBs within 6 months of study termination or completion

Institutional Review Board

This protocol and the subject ICD must be reviewed and approved by an IRB operating in accordance with local procedures and 21 CFR Parts 50, 56, and 812 before enrollment of subjects.

The Investigator is responsible for maintaining IRB approval for the study protocol and ICD and for keeping the IRB informed of protocol amendments and AEs in accordance with IRB requirements.

APPENDIX 1 SCHEDULE OF EVENTS AND PROCEDURES

PROCEDURE/EXAMINATION[1]	PREOPERATIVE & SCREENING (0 TO 60 DAYS PRIOR TO SX)	INTRA OPERATIVE (DAY 0)	1 DAY POSTOP (DAY 1-2)	1 WEEK POSTOP (DAY 5-10)	1 MONTH POSTOP (DAY 21-35)
Informed Consent / Demographics	X				
Ocular History	X				
Ocular Medications	X	X	X	X	X
Cohort selection: 1 or 2	X				
Surgical Procedure: Type of viscoelastic used, total procedure time, lens removal time, volume irrigation solution fluid used, anesthesia used, other surgical procedures performed, device malfunction/failures, Pre-segmentation instrument used, MICOR 304 model information, ease of surgery		X			
Cataract type and grade	X				
Manifest Refraction	X			X	X
Pinhole VA at Day 1			X		
BCVA Snellen	X			X	X
Dilated Pupil Size Measurement	X				
IOP (Goldmann Tonometry)	X		X	X	X
Slit Lamp Biomicroscopy	X		X	X	X
Dilated Fundus Exam / C:D ratio assessment	X				X
Central Corneal Thickness	X		X	X	X
Macular OCT (optional)	X		X	X	X

AE Assessment		X	X	X	X

1 All procedures/examinations will be performed on the study eye only

APPENDIX 2 EXAMINATION PROCEDURES, TESTS, EQUIPMENT AND TECHNIQUES

[redacted]

[redacted]

[redacted]

APPENDIX 3 WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious AEs. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects

must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition

to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo, or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.