

AMERICAN BURN ASSOCIATION
MULTICENTER TRIALS GROUP

MANUAL OF POLICIES AND PROCEDURES

Version 1.5

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Revision History

December 7, 2007: First draft distributed to Steering Committee members

December 9, 2007: Draft revision by the Steering Committee

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April 11, 2008: Revisions completed; version 1.5 submitted.

SECTION 1: INTRODUCTION AND OVERVIEW

1.1. Introduction:

The quality of clinical care has been shown to improve when prospective, randomized, clinical trials are performed according to prescribed guidelines. Such clinical trials generate the evidence necessary for establishing practice guidelines and standards, now recognized universally as critical for the insurance of maintaining high quality of care throughout specialty centers. The American Burn Association has committed itself as a professional organization to the creation of practice guidelines for burn care. However, this endeavor depends upon the successful completion of multicenter clinical trials, performed in a collaborative manner throughout the burn centers in North America. To this end, the ABA has formed the Multicenter Trials Group.

This manual outlines the general policies and procedures for operations of the Multicenter Trials Group (MCTG) of the American Burn Association (ABA). The purpose of this manual, and of the group, is to facilitate the design, performance, and reporting of the highest-quality clinical trials by members of the ABA, and to provide a mechanism whereby ABA members can participate in clinical trials. We hope that these policies and procedures will also help ensure fairness, ethical conduct, and protection for trial participants and their institutions, and for study subjects. In addition, they will also maximize the likelihood of success and support efficient use of resources. While some procedures are specified in some detail in this manual, we recognize that every study will have specific details which may not be covered by these policies, or which may require deviation from them.

1.2. History:

1.2.1. Initial Efforts:

The Multicenter Trials Group (MCTG) of the American Burn Association (ABA) began in 2000 with an informal meeting at the ABA annual meeting in Las Vegas. At that time, discussion centered on initially performing retrospective reviews of burn-related problems, with the goal of someday conducting multicenter clinical trials.

Good progress was made from this starting point. Within a year, the group had completed its first retrospective review of toxic epidermal necrolysis (TENS) in burn units, and data was presented at the 2001 ABA meeting in Boston. The following year (2002) a second abstract on management of purpura fulminans, was presented, and three more abstracts were presented the following year. In 2005 we presented the results of our first clinical trial of the use of oxandrolone in adults with major burn injuries.

The group has met at least twice yearly since then, and gradually become more organized. In 2005 a steering committee was elected, and a set of bylaws created and approved by the ABA Board of Trustees. A website was formed by the ABA, and is now used as our official medium of communication.

At this time (April, 2008) we have over 100 individual members, and 54 burn centers, registered through the website.

1.2.2. Mission Statement:

The American Burn Association Multicenter Trials Group is dedicated to optimizing the outcomes of care for burn injuries through multicenter evidence-based research. The ABA-MCTG will provide the leadership, education and, through the ABA, the infrastructure needed to facilitate research collaboration and information exchange among researchers, burn care providers, and the communities they serve.

1.2.3. The Search for Funding

The conduct of clinical trials is expensive and external funding for the administration of multicenter trials is imperative for the success of a group such as the ABA-MCTG. As part of our efforts to present a rationale for why funding for the infrastructure was necessary to support clinical trials in the burn community, a "consensus conference" was held by the ABA in the autumn of 2006 to define our current "state of the science", and formulate clear directions for future research. The conference was funded mainly by the American Burn Association, but with additional support from some of the conference co-sponsors. Conference co-sponsors included: NIDRR; Shriners Hospitals for Children; U.S. Army Medical Research & Material Command; the VA; and the National Institute for the General Medical Sciences, and was attended by ABA members, as well as representatives from the NIH, CED, and other agencies.

The first day of this three-day conference was devoted to a review of the state of the science in burns. Topics included clinical research, inhalation injury, burn resuscitation, inflammation and sepsis, nutrition and metabolism, and wound healing. On the second day, a comprehensive review of burn rehabilitation was performed. The third day was devoted to an editors' forum, and plans for re-defining burn research. Results of the conference have been published in the July/August, 2007 issue of the *Journal of Burn Care and Research*. Summaries of the findings of each session can also be found on the American Burn Association's Website (www.ameriburn.org)

Following this conference, at the subsequent ABA National Leadership Conference in Washington, D.C., the ABA sought political support for such funding. Thanks to the

strong support of Senator Barbara Boxer (D-CA), a funding request was submitted and approved through the Department of Defense appropriations process (additional support was also provided by Representatives Matusi (D-CA) and Lundgren (R-CA). As of April, 2008, the actual funds have not yet been appropriated to the ABA and are going through the DOD process. This funding will provide for creation of infrastructure for multi-center trials burn research, not the actual funding of any particular multi-center trial.. Based on a preliminary favorable review, the Steering Committee has already met to plan infrastructure design. Unrelated to the above infrastructure funding, a grant submitted, through the ABA by Dr.Tina Palmieri will fund a clinical trial of transfusion thresholds in burn patients. This grant is also approved tentatively, and should become the first large-scale clinical trial in our group. An additional grant, also submitted through the ABA by Mr. Reg Richard, will fund burn rehabilitation research, and be organized at least partly through the MCTG.

With this promising start, the MCTG hopes to be helping to perform large clinical trials soon. In addition, however, we recognize the need to continue to support smaller trials, retrospective reviews, conferences, and communications among members of the ABA. A section of this manual will be devoted to these efforts as well.

1.2.4. Publications to date (December, 2007)

1. Palmierei, TL, Greenhalgh, DG, Saffle, JR, Spence, RJ, Peck, MD, Jeng, JC et al. A multicenter review of toxic epidermal necrolysis treated in US burn centers at the end of the 20th century. *J Burn Care Rehabil*, 2002;23:87-96.
2. Warner, PM, Kagen, RJ, Yakuboff, KP, Kemalyan, N, Palmieri, TI, Greenhalgh, DG et al. Current management of pupura fulminans: a multicenter study. *J Burn Care Rehabil*, 2000;24:119
3. Kagan, RJ, Gamelli, R, Kemalyan, N, Saffle, JR. Tracheostomy in thermally-injured patients: does DRG 483 estimate resource use and hospital costs? *J Trauma*, 2004;57:861-6
4. Palmieri, T, et al. Blood transfusion in burns: what do we do. *J Burn Care Rehabil* 2004;25:71
5. Wolf, SE, Edelman, LS, Kemalyan, N, Donison, L, Cross, J, Underwood, M, et al. Effects of oxandrolone on outcome measuremes in the severely burned: a Multicenter prospective randomized double-blind trial. *J Burn Care Rehabil*, 2006;27:131-9.
6. Palmierei, TL, Caruso, DM, Foster, KN, Cairns, BA, Peck, MD, et al. Effect of blood transfusion on outcome after major burn injury: a multicenter study. *Crit Care Med*, 2006;34:1602-7
7. Palmieri, T, et al. Effects of a restrictive blood transfusion policy on outcomes in children with burn injury. *J Burn Care Rehabil* 2007;28:65
8. Ballard, J, Edelman, L, Saffle, J, Sheridan, R, et al. Positive fungal cultures in burn patients: A multicenter review. *J Burn Care Rehabil* in press.

SECTION 2: ORGANIZATION OPERATIONS AND POLICIES

2.1. General Operating Policies

2.1.1. Purpose:

These policies have been developed in order to help optimize the safety, efficiency, fairness, and adherence to rigorous scientific principles in the performance of clinical trials and other research by members of the American Burn Association. The following sections outline the general operating policies of the MCTG, its relationship to the American Burn Association (ABA), the responsibilities and organization of committees, and other functioning bodies during performance of clinical trials. Following sections also outline specifics of the performance of research within this framework.

2.1.2. Regulatory Compliance:

Participants in MCTG-sponsored trials or projects are expected to comply at all times with Good Clinical Practice (GCP) as defined by Title 21 of the Code of Federal Regulations (CFR), International Committee on Harmonization (ICH) guidelines, and all other applicable regulations regarding the conduct of clinical trials, as well as the Federal Regulation for Protection of Human Subjects (HRSA Circular No. 96.05, Code of Federal Regulations Title 45 Part 46 [45 CFR Part 46], and the Belmont Report).

Participants in MCTG-sponsored trials or projects must also agree to comply with the policies and procedures set forth in this manual. Compliance is the responsibility of all participants; any violation of these policies should be reported to the Steering Committee, and could result in withdrawal of MCTG-sponsorship of specific projects.

In addition, it will be the responsibility of all participants in MCTG-sponsored trials or projects to comply at all times with the policies and procedures of their individual institutions, granting agencies, and other oversight bodies. This includes obtaining Institutional Review Board (IRB) approval for any projects involving human subjects. These IRB's retain authority to regulate the performance of clinical research within their institutions. Any perceived conflicts between institutional regulations and the policies and procedures of the MCTG should be reported to the Steering Committee. It is the responsibility of the individual investigators, and not the MCTG, to resolve any conflicts regarding compliance with institutional policies and procedures.

2.1.3. Enforcement of compliance.

If participants are found to be noncompliant with any required regulations or policies in a manner which could impact research subject well-being or the conduction of clinical trials in accordance with GCP and/or established protocols, the Steering Committee has the right to enforce disciplinary action against those participants. Depending on the nature and funding of the trial, this disciplinary action might include: expelling individual investigators or centers from participation in MCTG-sponsored trials, stopping enrollment of patients in trials, or notifying responsible Principal Investigators (PI's) of these occurrences. The Steering Committee also retains the right to withdraw sponsorship of the Multicenter Trials Group from ongoing projects. Some of these responsibilities may

be contracted out to appropriate third-parties. Examples of noncompliance include, but are not limited to, inadequate documentation of adherence to stated safety and regulatory mandates, falsifying documentation, or any other action that puts at risk the safety and respect for rights of the human subjects involved.

2.2. Creation and Amendment of Policies and Procedures

This manual has been created as a guideline for the activities of the MCTG, and the performance of clinical research by participating ABA members. The Steering Committee will be responsible for reviewing and updating this procedure manual at least yearly, and for considering any changes recommended by committees or individual members. Changes to these policies and procedures can be performed by a simple majority vote of the Steering Committee.

A current version of this manual will be maintained on the ABA-MCTG web site, and can be obtained from the Steering Committee, or from the ABA Central Office.

Participation in day-to-day activities of the MCTG and its member groups do not require specific approval of the Steering Committee. However, any deviation from these procedures, or any activity, although not specifically covered by these procedures but which is felt to have a potential impact on patient safety, patient care, or the performance of ongoing trials, must be reported to and approved by the Steering Committee, as well as by any third-party entity the ABA may contract with to perform such functions.

2.2.1. Bylaws:

A separate set of Bylaws for the Multicenter Trials Group of the American Burn Association has been created, and is included as an appendix to this manual. The ABA-MCTG Bylaws are also available on the ABA Web Site (<http://www.ameriburn.org>). Amendment to the bylaws requires a majority vote of the members of the MCTG present at any annual meeting, as well as by the ABA Board of Trustees.

2.3. Membership, Meetings, and Communication

2.3.1. Membership in the MCTG:

Membership in the Multicenter Trials Group is open to any active member of the American Burn Association. Members may serve on committees, vote in elections and for regulatory changes, and participate in research activities. Individuals who are not members of the American Burn Association may participate in research and other activities on the invitation of the Steering Committee, Committee Chairs, or Principal Investigators, but may not vote or hold office in the MCTG.

2.3.2. Annual Meeting:

The Multicenter Trials Group will hold an open meeting during each annual meeting of the American Burn Association. This meeting will be open to all ABA members. Information about ongoing trials, solicitation of participation, and voting on any outstanding issues may take place at this time. Announcements of changes to this policy and procedures manual will also be made at this time.

2.3.3. Other meetings:

The Steering Committee of the MCTG will hold additional meetings throughout the year as needed. Any member who wishes to present a topic for discussion at such a meeting may contact the chair of the steering committee of the MCTG.

2.3.4. Communications:

The MCTG will maintain a website accessible through the American Burn Association's website (www.ameriburn.org). This website will be the location for all routine communications regarding MCTG activities, including committee structure and membership, minutes of public meetings, the status of all ongoing projects, and all publications and grants. A copy of these policies and procedures, and the bylaws of the MCTG, will be maintained on this site as well. This site will also contain a mechanism for contacting the Steering Committee, and the ABA Central Office.

Committee meetings may be held in person, by telephone, or by video-conferencing. Written minutes from annual meetings will be retained by the Secretary of the Steering Committee, and forwarded to the Board of Trustees of the American Burn Association.

2.4. Grievances:

Grievances regarding activities within participating institutions should first be addressed with the participant's institution. Subsequent requests for assistance resolving intra-institutional conflicts may be made to the MCTG Steering Committee. However, the MCTG is not responsible for resolving grievances within participating institutions.

Grievances regarding activities within the functions or structure of the MCTG should be reported to the Chair of the MCTG Steering Committee. Should further action be deemed necessary by the participant, appeals may be made to the Board of Trustees of the ABA.

2.4.1. Grievances reported to Steering Committee

Any member or participant may report a grievance regarding noncompliance with policies and procedures, violation of study protocols, or other administrative issues to the Steering Committee. Grievances must be made in writing, and posted using certified mail delivery. Grievances may be initiated by electronic mail (email), but only if they are immediately followed by written copies. They may be made anonymously, but with the understanding that this limits the ability of the Steering Committee to resolve them. Any grievance made to the Steering Committee will be reviewed and responded to within 30 days if possible. Report of the grievance and its resolution will be sent to the parties involved.

2.4.2. Patient Safety

Any member who perceives a threat to patient welfare or safety as a result of protocol violations or noncompliance during performance of a specific clinical trial should report that concern immediately to the Data Safety Monitoring Board (DSMB) or to the Steering Committee or both, whose functions may be contracted out to an appropriate third-party, which would function in coordination with the DSMB of the MCTG, of the study involved (described below), as well as the Steering Committee. . The DSMB will have jurisdiction over resolution of grievances regarding direct threats to patient welfare. Activities of the DSMB will be reviewed by the Quality Assurance, Safety and Regulatory Affairs Committee, and as such all such reported will ultimately be reviewed by the MCTG Steering Committee.

2.4.3. Grievances regarding Steering Committee: If a grievance involves a Steering Committee member, that member will be excused from deliberations regarding resolution of the grievance. If the remaining members of the Steering Committee are unable to reach an accord regarding disposition of the grievance, the current ABA President will be asked to participate in the deliberations and file the deciding vote.

2.4.4. Unsatisfactory resolution of grievances: Any member filing a grievance who feels that the response of the Steering Committee has not been satisfactory, including grievances regarding the Steering Committee itself or its members, may contact the Board of Trustees of the American Burn Association,

2.5. Organizational Structure

The organizational structure of the MCTG is outlined in Figure 1. The MCTG is organized within the membership of the American Burn Association. On behalf of the membership of the American Burn Association, the Board of Trustees has oversight responsibility for MCTG activities, including but not limited to the membership, name, and financial affairs of the American Burn Association.

The primary administrative body of the MCTG is the Steering Committee. The Steering Committee is responsible for reviewing protocols for clinical trials, and for approving protocols for performance under MCTG sponsorship. The Steering Committee will evaluate and monitor the conceptualization, performance, and reporting of clinical trials and other research. The committees each have responsibility for assisting in the performance of some aspect of the clinical research process. Their specific duties are outlined below.

Primary responsibility for each clinical trial will rest with the Principal Investigator (PI), who will be approved by the Steering Committee. The PI will be responsible for establishing protocols, conducting research, training and supervising site investigators, monitors, and coordinators, and preparing and reporting study results. The Steering Committee will monitor performance of each trial, and interact with the PI both to serve as a resource as well as to corroborate completion of the PI's responsibilities.

In addition, the PI will be responsible for interaction with the activities of a Data Safety Monitoring Board (DSMB), if such board is required for the study. The Steering Committee, and

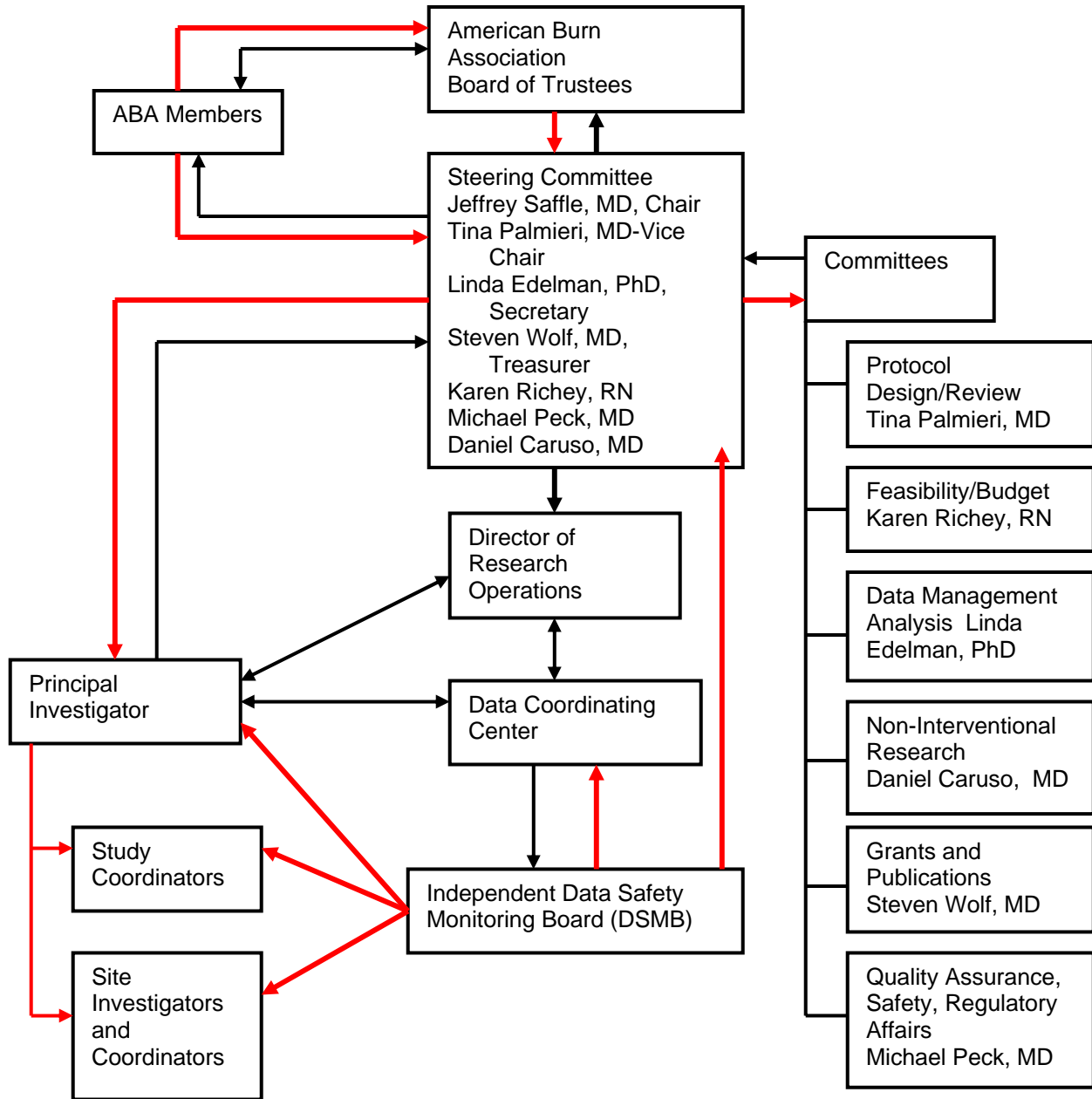
or granting agency, will determine if a study requires an independent DSMB. The Steering Committee must approve the members of the DSMB for any MCTG-sponsored project. The DSMB, whose primary functions may be contracted out to an appropriate third-party and work in conjunction with a similar MCTG committee, will have independent authority to review compliance and appropriateness of study protocols, subject enrollment and safety, and data collection and analysis. Section 4 describes the DSMB in more detail.

2.5.1. Director of Research Operations:

A Director of Research Operations (DROP) to assist investigators with oversight and coordination of day-to-day performance of clinical trials may be a contracted third-party approved by the MCTG and the ABA, and will report to the Chair of the Steering Committee. Qualifications for the position will include experience with performance of clinical trials, data collection and analysis, interaction with DSMB's and IRB's, and expertise in clinical medicine. Certification as a Clinical Research Associate or similar credentialing will be required.

The DROP will act as the interface between the Steering Committee and the PI in the performance of clinical trials, and also assist with communications with individual site investigators and research coordinators, the DCC, and the DSMB.

Figure 1: Organizational Structure of the MCTG



SECTION 3: Committees:

The bylaws of the MCTG create six standing committees of the MCTG:

- A. Steering Committee
- B. Grants and Publications Committee
- C. Protocol Design and Review Committee
- D. Feasibility and Budget Committee
- E. Quality Assurance, Safety, and Regulatory Affairs Committee
- F. Data Management and Analysis Committee
- G. Non-interventional Studies Committee

3.1. The Steering Committee

3.1.1. Purpose:

The Steering Committee (SC) of the MCTG is the major administrative and regulatory body of the organization. The committee is responsible for each step in the process of performance of clinical research, including

- A. Developing, implementing, and enforcing policies and procedures for the successful performance of research within the MCTG.
- B. Developing and announcing research priorities for the ABA and MCTG.
- C. Assisting members in the conceptualization, creation, and performance of clinical research, especially multicenter clinical trials. This will include review and approval of research proposals, grants, and protocols, assessing the financial, clinical, and scientific feasibility of each project, assisting in the design of appropriate methodology and oversight of research protocols, monitoring ongoing clinical trials, helping to provide independent safety monitoring and data analysis for each project, reviewing and approving abstracts and publications, and reviewing accounting and expenditure of research funding.
- D. Providing education to ABA/MCRTG members in the successful performance of clinical research.
- E. Providing support to the ABA in interactions with funding agencies, regulatory oversight bodies, and industry.

3.1.2. Committee Membership

As stipulated in the bylaws, the Steering Committee will consist of seven members of the American Burn Association, no more than five of whom can be physicians. Members will be elected by the general membership, either at the annual meeting, or via the MCTG website..

3.1.3. Terms of Office

Each member of the Steering Committee will serve a term of five years, and these will be staggered so that no more than three members rotate each year. Members of the Steering Committee will be allowed to serve more than one concurrent five-year term.

3.1.4. Committee Officers

As stipulated in the bylaws, the Steering Committee members will elect a Chair, Vice-Chair, Treasurer, and Secretary.

3.1.4.1. Chair

Duties of the ABA-MCTG Steering Committee Chair are primarily those of overseeing the operation of ABA-MCTG, including coordinating and presiding at Steering Committee meetings, and maintaining ongoing communications with all other entities, including the ABA Board of Trustees.

3.1.4.2. Vice-Chair

Duties of the Vice-Chair include assisting the Chair with ABA-MCTG responsibilities, as deemed necessary. The Vice-Chair may officiate at meetings in the temporary absence of the Chair. If the Chair becomes unable to perform his or her duties as determined by a majority of Steering Committee members, the Vice-Chair will assume the Chair's responsibilities and will initiate a vote by the Steering Committee to select a new Chair.

3.1.4.3. Secretary

The ABA-MCTG Secretary will be responsible to ensure that careful and authentic records of Steering Committee proceedings are kept. These duties will include carefully reviewing Steering Committee minutes and summaries for their accuracy and integrity.

The Secretary will also maintain an updated list of all committee officers and members and ensure that a copy of the ABA-MCTG bylaws is available at all Steering Committee meetings.

The Secretary will be responsible for posting and publishing Steering Committee minutes and communications to the ABA and the MCTG websites, as directed by the committee.

3.1.4.4. Treasurer

The ABA-MCTG Treasurer will be responsible for managing any and all financial dealings of the ABA-MCTG in cooperation with the ABA Board of Trustees. The treasurer, in conjunction with the ABA Central Office, will prepare and submit a budget to

the Board of Trustees for funding of Steering Committee and MCTG activities, meetings, and other expenses.

3.1.5. Ad Hoc Members

The Chair may appoint other individuals, including non-ABA members, to attend Steering Committee meetings or provide technical support or advice or both. These ad hoc members may not vote.

3.1.6. Removal of Members

Any member of the Steering Committee may be removed from the SC in one of two ways:

- By majority vote of the remaining members of the SC
- By a majority vote of the Board of Trustees at the annual meeting.

3.1.7. Meetings

3.1.3.1. Annual Meeting: The Chair of the Steering Committee will preside over the open meeting of the MCTG held during each year's ABA annual meeting.

3.1.3.2. Other meetings: The Steering Committee will meet at least twice yearly, and more often as determined by the Chair and SC members. These meeting may be held using telephone conference calls or other electronic media.

3.1.3.3. Minutes: Minutes of the SC meetings will be made available by the Secretary to the SC members and the Board of Trustees of the American Burn Association. Deliberations and progress made by the committee will be summarized on the MCTG website.

3.2. Organization of Other Committees

3.2.1. Purpose: Each committee has a specified purpose and role in the performance of clinical research activities, stated in the appropriate section for that committee.

3.2.2. Committee Membership

3.2.2.1. Committee Chair: The Chair of each Committee will preferably be a member of the ABA-MCTG Steering Committee. The Chair will be appointed by the SC in accordance with the MCTG bylaws.

3.2.2.2. Chairperson's term: The Chair will serve a term not to exceed five years. One additional term will be permitted with the approval of a simple majority of the SC.

3.2.2.3. Committee members: Other members of the Committee will be appointed by the Chair, subject to the approval of a simply majority of the SC. Committee members will be members of the ABA. The Committee must contain at least three and no more than seven members. Additional ad hoc members who may not be ABA members can be appointed by the Committee Chair, with approval

of the SC for the purpose of providing technical expertise or advice; Ad hoc members may not vote.

3.2.2.4. Terms of members: Committee members will be appointed for terms not to exceed five years. Two terms will be permitted each member.

3.2.2.5. Removal of members: The Committee Chair will have the authority to remove members of the Committee for non-performance of duties or for other activities not consistent with the mission and values of the MCTG, with approval of a simple majority of the SC.

3.2.3. Committee meetings

3.2.3.1. Frequency: Each Committee will meet at least annually, during the annual meeting of the ABA. A report of that Committee's activities will be presented to the SC during the annual meeting as well.

3.2.3.2. Additional Meetings: Additional meetings of each Committee will be scheduled by the Chair as needed. These may include conference calls or electronic communications.

3.2.3.3. Minutes: Minutes of each Committee meeting will be kept and made available to the SC and Committee members.

3.2.3.4. Quorum: At any meeting of any Committee, a simple majority of members will constitute a sufficient quorum for business to proceed.

3.2.4. Committee Business/Failure to Complete Assignments

Each Committee will have specified responsibilities to complete during the process of reviewing grants, protocols, and/or manuscripts, and supervising the conduct of clinical trials. Specific committee responsibilities are outlined in the following sections. The SC will set deadlines for the completion of each Committee's tasks. Failure to complete assignments within this period will be grounds for the SC to assume that Committee's function, reassign it, or reject the subsequent report of that Committee.

3.3. Grants and Publications Committee

3.3.1. Purpose: The purpose of the Grants and Publications Committee (GPC) includes:

3.3.1.1. Supporting and guiding members in the creation of grants for funding of multicenter trials and other clinical research projects within the MCTG structure. The Committee will determine if the grant appears to be feasible, ethical, and addresses a clinical question of sufficient importance and controversy to be worth conducting. The decision of the GPC will be presented to the SC by the GPC Chair for final deliberation.

3.3.1.2. Creating appropriate grants at the direction of the Board of Trustees or the Steering Committee.

- 3.3.1.3. Reviewing all publications stemming from MCTG activities for appropriateness and adherence to ethical practices.
- 3.3.1.4. Assisting authors to write manuscripts stemming from MCTG activities.
- 3.3.2. **Membership:** Membership of the GPC will adhere to the guidelines for Committee membership provided above. Committee members should have experience with writing and obtaining grants from federal agencies, industry, and private foundations, and experience in writing and publishing manuscripts in biomedical journals. One or more experts in statistical analysis, pharmacy practice, or other disciplines may be included as regular or *ad hoc* members of the GPC.
- 3.3.3. **Submission of Grants, Manuscripts, and Abstracts for Review.** Grants, manuscripts, and abstracts will be submitted for review, and the review process will be completed according to the steps outlined in Section 4.
- 3.3.4. **Creation of Grant Proposals by the Committee**
 - 3.3.4.1. **Circumstances:** The primary role of the GPC is to assist ABA members in producing grants or publications that involve the MCTG. However, the GPC may also generate new grant proposals or publications, with the approval of the SC, under any of the following circumstances:
 - 3.3.4.1.1. **New Proposal and Grant Initiatives:** If the SC believes that a specific study should be undertaken but that such study has not yet been proposed by an ABA member, the GPC can be directed to investigate the creation of a research proposal and grant application. However, all proposals and grants must have at least one clearly identified Principal Investigator (PI). In this circumstance it will be the responsibility of the SC to identify a PI who will be involved in all phases of conduction of the study. Confirmation of acceptance of responsibility by the PI must be obtained before planning for any study can proceed. Such new proposals and grants are required to be approved through all the usual processes of proposal and grant evaluation by other Committees and the SC, as outlined elsewhere.
 - 3.3.4.1.2. **Internal Grants:** The preparation of grants which involve funding or re-funding of MCTG structure, such as the Data Coordinating Center, or funding for MCTG employees. In this circumstance the Chair of the SC will serve as PI, and be involved in all phases of the production and conducting of the grant. Such new grants are required to be approved through all the usual processes of grant evaluation by other Committees and the SC, as outlined elsewhere, as well as being in conjunction with the ABA Board and Central Office.

3.3.4.1.3. Progress Reports: The preparation of progress reports and other documents relating to ongoing grants in which the SC Chair is the PI will be the primary responsibility of the Chair of the Steering Committee. However, the GPC will assist the SC when requested.

3.3.4.1.4. Failure to Publish: If PI's of MCTG projects fail to deliver manuscripts of completed work within the deadline established by the MCTG and the PI, the Steering Committee will have the right to assign the writing of such manuscripts to the GPC for completion and publication. This should be done with the approval of the original PI. If this approval is not obtained, the SC will have the right to approve such a manuscript for publication, with clear explanation of the circumstances of the preparation of the manuscript. In this event, the process of creating the manuscript, and the manuscript itself, must be approved by the Board of Trustees of the ABA.

3.3.5. Decision Guidelines

The primary consideration of the GPC for study proposals, grant applications, and abstracts and manuscripts, is the determination of adequate scientific rigor in the analysis of data, the proper construction of study design, and the feasibility of determining meaningful outcomes.

Secondary considerations include the appropriateness of authors' conclusions, the perceived impact of the study, and the scientific merit of the study for the burn community.

Additional considerations include quality of prose and effectiveness of written expression, the adequacy of review of published literature, and the effective use of tables and graphs.

3.4. Protocol Design and Review Committee

3.4.1. Purpose: The purpose of the Protocol Design and Review Committee (PDRC) includes:

3.4.1.1. Assisting ABA/MCTG members in creating protocols for multicenter research. Protocols will be reviewed for validity of hypotheses, appropriate methodology, safe-guards to patient welfare, adherence to GCP guidelines, and necessary statistical power and rigor.

3.4.1.2. At the direction of the Steering Committee, creating protocols for conducting clinical trials under the supervision of the MCTG.

- 3.4.1.3.** Reviewing protocols submitted by industry sponsors or other outside agencies for appropriate content, feasibility, and relevance to the missions of the MCTG and the ABA.
- 3.4.2. Membership:** Membership in the PDRC will adhere to the guidelines for Committee membership described above. Members should be selected for experience and expertise in the design and conduct of clinical trials. One or more members should have expertise in statistical analysis as it pertains to protocol design. Other experts can be appointed as ad hoc members as needed.
- 3.4.3. Review of Protocols for Clinical Trials within the MCTG:** Clinical protocols will be submitted for review, and the review process will be completed according to the steps outlined in Section 4. The PDRC will assist individual investigators who wish to develop a clinical protocol for a trial. Usually, the first step in this process is submission of a study proposal to the SC. After approval of such a proposal, and identification of a Principal Investigator, the PDRC will be instructed to assist the investigator with development of a full protocol.
- 3.4.4. Creation of New Protocols by the Protocol Design and Review Committee**
At the direction of the Steering Committee, the PDRC may create new study protocols for performance by the MCTG. Such protocols will be performed to adhere to the outline in Section 4, and written to contain all of the key elements described.
- 3.4.4.1. Principal Investigator:** Each study protocol must have an identified Principal Investigator (PI) who will be personally involved in all phases of protocol design and writing. Co-Investigators may be appointed by the PI. The PI may be identified by the SC, or designated by the PDRC Chair. Acceptance of this responsibility by the PI must be confirmed before the protocol is created
- 3.4.4.2. Protocol Review:** A protocol designed primarily by the PDRC will be submitted to the SC for review, and then sent to other relevant committees in a manner identical to the process used for review of projects submitted by other MCTG members.
- 3.4.5. Decision Guidelines:**
The primary consideration of the committee for review of clinical protocols is determination of the proper study design to permit addressing a clinical question of importance with appropriate methodology to obtain necessary data. Secondary considerations include the safety of research subjects, ethical conductance of the project, fiscal feasibility, and availability of resources for performance of the project.

3.5. Feasibility and Budget Committee

- 3.5.1. Purpose:** The purpose of the Feasibility and Budget Committee (FBC) includes:

- 3.5.1.1. Assisting members in the preparation of grants or clinical protocols by evaluating the appropriateness and adequacy of budget considerations, assuring that funding sources are available, and helping to monitor the disbursement of funds for MCTG-sponsored research.
 - 3.5.1.2. Evaluating all grants or clinical protocols for feasibility, including the number and type of potential subjects, the resources available to conduct the research, and the adequacy of methodology to measure the outcomes appropriately and accurately.
 - 3.5.1.3. Monitoring the performance of clinical trials including fiscal soundness and appropriate expenditure of funds, adequate enrollment, and other issues related to the feasibility of the trial.
 - 3.5.1.4. Monitoring and accounting for expenditures of funds for MCTG clinical trials which are administered by ABA, including reimbursement for study centers and investigators, travel expenses, and hiring outside consultants. The FBC will assist in the preparation through the ABA Central Office and outside accounting/auditing representatives any financial reports which are required.
- 3.5.2. Membership:** Membership in the FBC should adhere to the guidelines for Committee membership provided previously. Members should be selected for experience and expertise in the administration of funded grant projects, the design and conduct of clinical trials, and general cost-accounting procedures. If a project being reviewed involves expenditure of funds administered by the MCTG, a representative from the ABA Central Office should be included as a member.
- 3.5.3. Review of Protocols for Clinical Trials within the MCTG:**
Clinical protocols will be submitted for review, and the review process will be completed according to the steps outlined in Section 4. Usually, the first step in this process is submission of a concept proposal to the SC. After approval of such a proposal and identification of a PI, the Logistics, Feasibility and Budget Committee will be instructed to assist the PI with protocol development.
- 3.5.4. Decision Guidelines:**
The primary consideration of the FBC for review of clinical protocols is determination of the proper construction of study design to permit completion of the project in a reasonable and predictable time with adequate resources to answer the proposed clinical question, and a budget to assure this. Additional considerations include the safety of research subjects, appropriateness of methodology, and ethical conductance of the project.

3.6. Quality Assurance, Safety, and Regulatory Affairs Committee

3.6.1. Purpose: The purpose of the Quality Assurance, Safety, and Regulatory Committee (QASRAC) includes:

- 3.6.1.1.** Assisting members in the creation of grants or clinical protocols addressing the safety of study subjects, the adequacy of quality assurance indicators, adherence to ethical standards, and appropriate compliance with all appropriate external regulations.
- 3.6.1.2.** Working with an appropriate contracted third-party DSMB (such as the DCC at the University of California – Davis) to coordinate their functions. Work with the third-party DSMB during the performance of clinical trials, monitoring ongoing trials to ensure the safety of participants, ethical conduct of research, and adherence to regulatory guidelines. The committee will have the authority to recommend alternations in protocol design, enrolling of participants, or other aspects of the conduct of MCTG-sponsored trials.

3.6.2. Membership: Membership in the QASRAC will adhere to the guidelines for Committee membership provided previously. Members should be selected for expertise in design and conduct of clinical trials, familiarity with Institutional Review Board requirements, medical ethics, or biostatistics. Appropriate lay members including attorneys and clergy can be included as ad hoc members, depending on the nature of the projects being reviewed.

3.6.3. Review of proposed clinical protocols

Clinical protocols will be submitted for review, and the review process will be completed according to the steps outlined in Section 4 at the direction of the SC as outlined previously.

3.6.4. Decision Guidelines:

The primary consideration of the QASRAS for review of clinical protocols is determination of the proper construction of study design to address safe and ethical treatment of research subjects, provision of adequate monitors for quality assurance, ethical conductance of the study, and adequate compliance with regulatory oversight. Secondary considerations include adequate methodology, instruments, and organization to facilitate collection of data needed to address the study question, fiscal feasibility, and availability of resources for performance of the project.

3.7. Data Management and Analysis Committee

3.7.1 Purpose: The purpose of the Data Management and Analysis Committee (DMAC) includes:

3.7.1.1. Assisting members in the creation of grants or clinical protocols by helping design data collection instruments that are adequate for the measurement of results and outcomes.

3.7.1.2. Working with the DCC to set up standardized data collection methodology for MCTG-sponsored research.

3.7.1.3. Reviewing the data collection and statistical analysis performed by the DCC.

3.7.2. Membership: Membership in the DMAC will adhere to the standards for Committee membership provided previously. Members should be selected who have experience and expertise in design and conduct of clinical trials, biostatistics, computerized data recording and outcomes analysis. Additional experts in statistics can be included as ad hoc members as needed.

3.7.3. Submission of Clinical Protocols for Review:

Grants, manuscripts, and abstracts will be submitted for review, and the review process will be completed according to the steps outlined in Section 4 at the direction of the Steering Committee as outlined previously.

3.7.4. Decision guidelines:

The primary consideration of the DMAC is to review clinical protocols for determination of the proper study design to permit collecting adequate objective, accurate, and reproducible data for addressing the clinical question of the study, and detect both anticipated and unanticipated adverse and favorable outcomes of interventions. Additional considerations include the safety of research subjects, ethical conductance of the project, fiscal feasibility, and availability of resources for performance of the project.

3.8. Non-Interventional Studies Committee

3.8.1. Purpose: A number of types of non-interventional research can be conducted with relatively little expense, and with protocols that are not as detailed or restrictive as those required for interventional trials. The purpose of the Non-Interventional Studies Committee (NISC) includes:

3.8.1.1. Assisting members in the design and conduct of clinical studies that do not involve therapeutic interventions applied to patients. Such studies include retrospective multicenter reviews, prospective data collection or registries, clinical practice guidelines, reports of quality assurance or improvement activities, and other data review procedures.

3.8.1.2. Working with the other Committees of the MCTG and the SC to help investigators identify funding sources, create data collection instruments, obtain IRB authorizations, perform data collection and analysis, assist with publications, and facilitate other procedures relating to the performance of non-interventional trial research.

3.8.2. Membership:

Membership in the NISC will adhere to the standards for Committee membership provided previously. Members should be selected who have experience and expertise in design and performance of chart reviews, clinical research, IRB compliance, and data analysis. Additional experts in specific components of clinical research can be included as ad hoc members as needed.

3.8.3. Performance of Non-Interventional Research:

Protocols for non-interventional research submitted to the MCTG for approval and performance should be submitted by the NISC to the Steering Committee as outlined in Section 4. Any assistance with funding, data collection or analysis, research coordination, or other performance issues should be approved by the SC at the beginning of the project.

3.8.4. Decision Guidelines:

The primary consideration of the NISC for review of clinical protocols is determination of the proper study design to permit collecting adequate objective, accurate, and reproducible data for addressing the clinical question of the study. Secondary considerations include the safety of research subjects, ethical conductance of the project, fiscal feasibility, and availability of resources for performance of the project.

SECTION 4.0. DESIGN AND PERFORMANCE OF CLINICAL TRIALS

4.1. General Policies for Clinical Trials

4.1.1. Introduction: This chapter provides a general overview of the processes by which research proposals are developed into protocols for clinical trials, and by which those trials are conducted with the assistance of the MCTG. This is not intended to be a comprehensive discussion of the theory or methodology of clinical trials. Additional information regarding study design, methodology, safety, and reporting of data will pertain to each specific trial, and be considered by the appropriate committees, the principal investigator(s) and study participants, and be incorporated into specific study protocols. Adherence to widely-accepted guidelines for Good Clinical Practice, protection of human subjects, and other regulations is assumed, and will be required by PI's.

The following sections describe how the MCTG would be involved in all phases of study proposal, design, and performance, but specific areas may not apply. For example, industry-sponsored protocols may be designed internally or by clinical research organizations. Involvement of the MCTG in each phase of this process will be stipulated as protocols are instituted, and specified in agreements with investigators.

4.1.2. Principal Investigator: Each clinical trial will be directed by a designated Principal Investigator (PI) who will be identified and approved by the Steering Committee of the MCTG. The PI will be responsible for all phases of study design and performance, and bear primary and personal responsibility for conducting the trial. In multicenter studies, there will be a Lead PI for the entire study, but individual PI's will be appointed for each study site, with the approval of the Lead PI, and the Steering Committee.

Each PI will be required to sign a contract with the MCTG agreeing to comply with MCTG guidelines, and recommendations of MCTG committees and other oversight groups in creating and conducting clinical trials.

4.1.3. Approval of Study Protocols: Any grant proposal, clinical protocol, or manuscript under consideration for performance using MCTG resources or personnel, or conducted with the cooperation or bearing the name of the MCTG or the ABA must be submitted to the Steering Committee for review and, through the SC, to each relevant Committee. Each Committee will review the document and make recommendations regarding their specific aspect of clinical research to the Steering Committee. According to the guidelines established for each Committee, as above, the PI may be asked to revise the document one or more times, and re-submit it for subsequent review. Protocols not approved by the SC cannot be performed under the sponsorship of the MCTG.

4.1.4. Steering Committee Oversight

Clinical trials approved by the MCTG or conducted with MCTG approval will be monitored by the SC and subsidiary committees throughout their duration. In the event of perceived problems with the performance of trials, the SC will have authority to perform any of the following:

- 4.1.4.1. Removal of Investigators:** The SC may remove its endorsement of the PI of an MCTG-sponsored trial if it becomes known to the SC that individual fails to adhere to MCTG policies and procedures, or deviates significantly from trial protocols in a manner that compromises scientific validity, Good Clinical Practices, or patient safety and welfare. This can apply either to Lead PI's or to site investigators or both, as indicated. In the case of an MCTG-funded trial, the SC may appoint another PI to assume responsibility for the study or it may stop the study. In the case of externally-funded studies, the SC may elect to formally remove the study from MCTG and ABA sponsorship. The SC will enforce and act upon the recommendations of subsidiary committees in this regard. In such circumstances, the SC will notify appropriate federal funding and oversight agencies of this decision. Further, the SC will have the authority to disqualify investigators or other study participants from participating in other MCTG-sponsored activities as deemed necessary, for a period of time considered appropriate.
- 4.1.4.2. Cessation of Study Enrollment/Disbursement of funds:** Further, the SC will have the authority to stop patient enrollment in trials in which these issues become apparent, and recommend that disbursement of funds, which are controlled by the ABA, for conducting a trial be withheld until compliance with SC recommendations and oversight is restored.
- 4.1.5. Reporting of Data:** Each study PI will be required to report the findings of their study to the SC within a time frame specified, and to prepare an appropriate manuscript(s) for publication if so directed. If the study is performed with MCTG financial support, and the PI fails to complete these assignments, the SC will have authority to take control of study data and create a manuscript of study findings. Authorship for all manuscripts will adhere to recognized guidelines for co-authorship, outlined below.
- 4.1.6. Conflict of Interest.** By nature, the ABA and MCTG are composed of a limited number of specialized clinicians. It is therefore almost certain that some Committee members may also play significant roles in the creation or performance of clinical protocols under review. Committee members who perceive a conflict of interest between their responsibilities for the Committee and their role in performance of the clinical trial should inform the Committee Chair, and excuse themselves from deliberations and review of that protocol. They may be permitted to remain in the Committee meeting at the discretion of the Chair. The Chair has the authority to exclude Committee members from deliberations if he or she perceives that a potential conflict of interest exists.
- 4.1.7. Ownership of Data and Study Results**
The data generated during performance of a clinical trial conducted using the resources, personnel, or financial support of the MCTG, or conducted with the cooperation or bearing the name of the MCTG or the ABA will become the property of the ABA.. Use of study data by investigators in publications, presentations, grant proposals, and other uses will require the permission of the MCTG. Failure to obtain permission may justify

disqualification of the investigator from further involvement in MCTG-sponsored activities, retraction of publications, or formal requests to remove any reference to affiliation with the MCTG or ABA.

4.2. Protocol Development

4.2.1. What is a clinical trial?

As defined in the bylaws, the major purpose of the MCTG is to facilitate the design and performance of randomized, controlled trials of major therapeutic interventions within the American Burn Association. Most such trials will require multicenter participation owing to the relatively small size of burn centers, the requirement for significant sample sizes for statistical rigor and adequacy, the need for generalizability of results, and the desire to involve ABA members in clinical research. However, other types of clinical research, including retrospective (“chart review”) studies, and prospective, non-randomized or observational trials, will also be performed within the MCTG; methods for proposing and performing these types of research are described in section 5. The sections which follow describe in general the process of creating and performing a randomized, prospective, controlled multicenter trial.

4.2.2. Process of Protocol Development:

The process by which a hypothesis is developed into a workable and detailed protocol is described below, and summarized in Figure 4.1. This figure provides a general diagram of the steps involved, which may be modified as needed for specific protocols.

4.2.3. Study Concept Proposal:

All clinical trials will begin with submission of a proposal to the SC. Any ABA member interested in participating in such a project is encouraged to submit to any SC member a brief description of his or her idea, the major research question to be addressed, and the intervention to be tested. An example of a concept proposal form is contained in the Appendix. This form can be used either for a multicenter clinical trial or for any type of non-interventional trial. This submission will start the formal process of protocol development. In some situations this initial submission may be a detailed industry-sponsored protocol, a protocol for a trial which has been conducted in a single center, a meta-analysis of existing literature, or other format.

Concept proposals need not be more than three pages in length, and should include the following:

Background: A statement of the experience or data supporting definition of the clinical problem to be addressed.

Hypothesis: The question to be tested by the proposed trial.

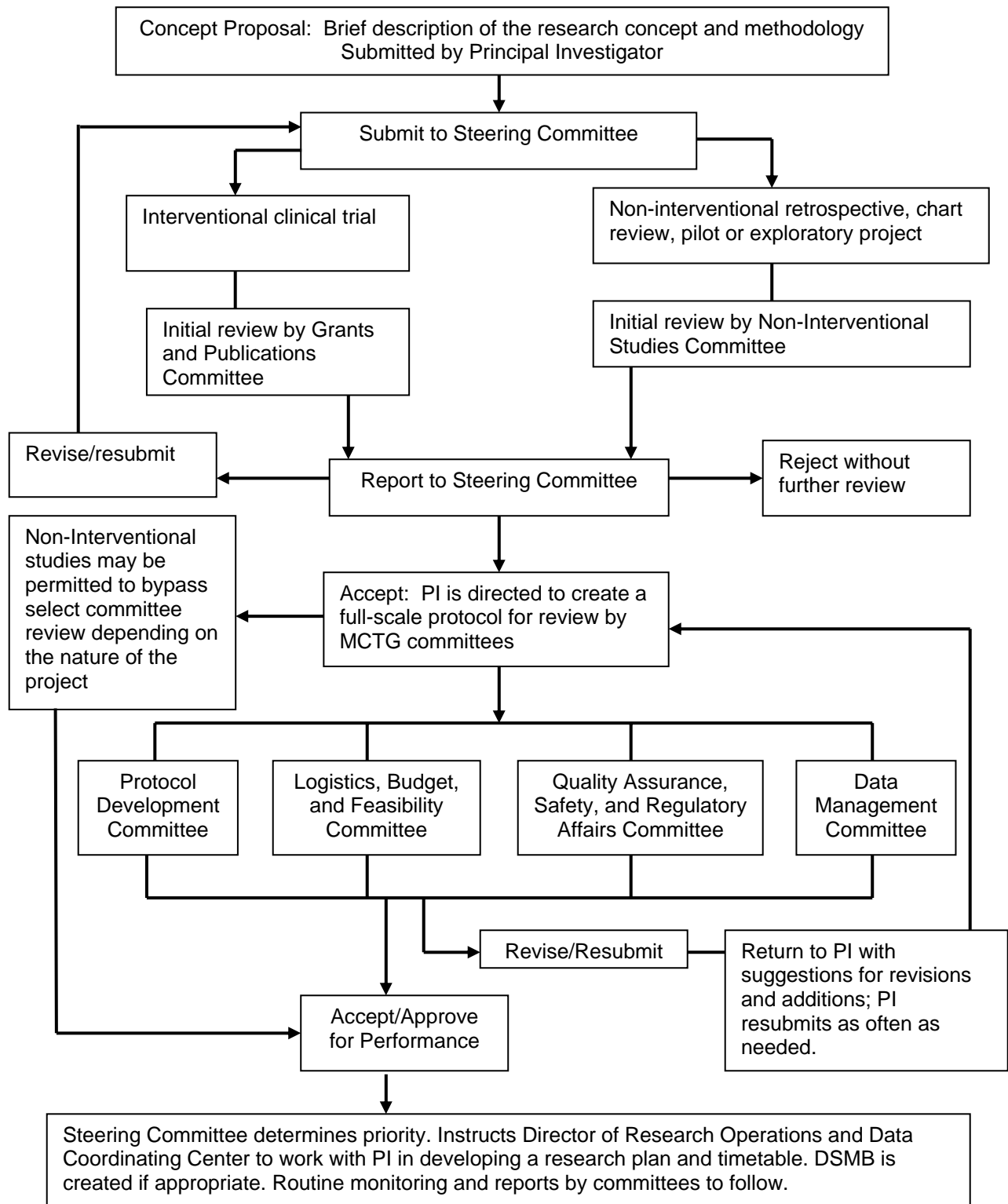
Methodology: A brief description of how the trial would be performed.

Budget: An estimate of the resources required to perform the trial

Principal Investigator: A PI who will assume primary responsibility for the design, performance, and results of the trial. In some circumstances a proposal

may be submitted of major importance to the burn care community for development by the MCTG. in that circumstance the SC will be responsible for recruiting and designating a PI.

Figure 4.1. Process of Development of a Protocol for Clinical Research



4.2.4. Preliminary Review by the Grants and Publication Committee: Concept proposals for clinical trials will be assigned to the GPC. The GPC Chair will assign at least two members to perform a full review of the proposal, and present their findings to a meeting of the GPC, which will be convened for that purpose. This review will be completed within 15 business days of receipt of the proposal. A decision regarding the proposal will require a vote of a simple majority of GPC members. The decision of the GPC will be reported to the SC.

Some proposals may be submitted as more fully-developed protocols, such as externally funded grants or industry-sponsored trials. These proposals will also be reviewed by the GPC, and a report forwarded to the SC.

Details regarding the development of non-interventional research are contained in Section 5.

4.2.5. Steering Committee Decision: Based on the report of the GPC, the SC will classify the proposal as follows:

Reject: The proposal does not address a problem of significant importance to justify a clinical trial, or is ethically or practically unfeasible, or requires resources which are not available. Proposals which are rejected will not be considered further by the MCTG, or be eligible for MCTG sponsorship.

Revise/Resubmit: A proposal which appears to have some merit, but includes some components which must be clarified or corrected before it can be considered acceptable, will be returned to the author for revision and resubmission to the GPC. Multiple revisions may be required before acceptance is granted.

Accept: A proposal which is accepted will be submitted for full review by all Committees of the MCTG.

This decision will be announced by the SC not more than 15 business days following receipt of the GPC's report. The vote of a simple majority of SC members will be required for any action.

The GPC's findings will be submitted as a report to the author of the proposal.

4.2.6. Creation of a Study Protocol/Committee Review: Proposals which are accepted by the SC will next move to design of a full-scale clinical protocol. The PI will write a detailed protocol for the performance of the study. This protocol will be submitted to each of the Committees of the MCTG as appropriate, and each will suggest revisions and additions to improve the protocol. It is emphasized that writing the protocol is the responsibility of the PI, but the Committees will help as much as possible to produce a protocol which is feasible, ethical, important, and cost-effective. This process may require a number of revisions until the protocol is accepted by each of the Committees.

Each committee will take no longer than 15 business days to review each revision and respond to the PI and the SC.

Each Committee will evaluate the protocol for content relevant to their specific topic, but general reviews for content, syntax, and feasibility will also be the responsibility of each Committee.

Specific evaluation criteria of the Committees include, but are not limited, to the following:

4.2.6.1. Protocol Design Committee Criteria:

1. Is the topic important enough to justify a clinical trial?
2. Are specific aims appropriate and clearly stated?
3. Is the hypothesis testable?
4. Are methods the best possible ones to answer the study questions, and are they feasible?
5. Has power calculation been performed appropriately, and is the sample size capable of being recruited and enrolled?
6. Has the PI demonstrated qualifications to conduct and supervise this trial? Are appropriate study coordinators available?

4.2.6.2. Logistics, Feasibility, and Budget Committee Criteria:

1. How will the study be organized and conducted? How will specific duties be assigned and performed? In the case of a multicenter trial, have participating centers and investigators been identified and recruited?
2. Is the methodology capable of being performed by the PI's center and each participating center?
3. Is the budget appropriate? Have all major budgetary items been considered and included? Is appropriate funding available to carry the study to conclusion?
4. Have appropriate methods for educating investigators and coordinators been created?

4.2.6.3. Quality Assurance, Safety, and Regulatory Affairs Committee:

1. How has the issue of quality assurance and accuracy in performance of the study been addressed? Are appropriate internal and external methods in place?
2. Is the study safe for subjects, and has it been designed in the safest possible way? Has subject confidentiality been assured? Have subject consent forms been designed appropriately?
3. Have all regulatory considerations been addressed, including Good Clinical Practices, Safety of Human Subjects, and IRB approval?
4. Is a rigorous mechanism for periodic reviews of patient outcomes, as well as definitions and reporting mechanisms for adverse events, been designed?
5. Can an appropriate Independent Data Safety Monitoring Board be identified and recruited?

4.2.6.4. Data Management and Analysis Committee:

1. Has the study been designed with appropriate statistical methodology, including power analysis, randomization and blindness, proposed statistical methods for data analysis, and definitions of significance?
2. Are the objectives of the study reflected in the data variables collected? Is there adequate definition of data variables to ensure uniform data collection between multiple sites?
3. Are the methods and forms for data collection appropriate, accurate, and safe?
4. Has the Data Coordinating Center reviewed the protocol, and agreed to perform data collection, storage, and analysis? Are appropriate hardware and software resources available to complete the study?
5. Has a primary study statistician been identified and recruited?
6. Are mechanisms in place for appropriate periodic reviews of data, including site visits, random compliance and accuracy checks, and access to data by the DSMB?

4.2.7. Final Approval

The protocol will be reviewed by each committee, and a report forwarded to the SC after each review cycle. When all committees have approved the final protocol, the SC will meet to review the final protocol for approval.

The ultimate content of the protocol is the primary responsibility of the PI. The PI is not required to make every change suggested by Committees during the process of protocol writing, but the final protocol must be approved by the SC before the trial can begin as an MCTG-sponsored project.

Following final approval, the protocol can then move forward. If the protocol is for a grant, the PI can submit the grant for funding with the support of the MCTG. If funding is already available, then performance of the trial can begin. Performance of clinical trials is described in Section 4.3.

4.2.8. Prioritization of Projects: Given the relatively small numbers of potential subjects, it is likely that only one or two prospective randomized controlled trials can be conducted at one time on similar populations (for example, children with smoke inhalation injury or adults with burns). Thus even some approved proposals will not be able to move quickly to implementation. The SC will have the authority and responsibility to assign priorities to specific proposals, and withhold permission to begin specific trials until appropriate resources are available to complete them. Prioritization of proposals will be based on clinical importance, feasibility, anticipated length of completion, and financial resources available.

4.2.9. Industry-Sponsored Projects: Clinical trials are often proposed by pharmaceutical companies interested in testing or demonstrating the efficacy of a new product. These

types of studies would be eligible for performance under sponsorship of the MCTG if they adhere to the following conditions:

- 4.2.9.1. The protocol for the clinical trial is approved by the Steering Committee. This includes the designation of the PI, creation and composition of the DSMB, and identification of the DCC.
- 4.2.9.2. The protocol includes a budget for all phases of performance of the trial, including compensation to the SC and other committees for time spent in developing and/or reviewing the protocol.
- 4.2.9.3. The SC, through the DROP, retains the opportunity to monitor the project as it is conducted, and review the data collection process.
- 4.2.9.4. The SC has the opportunity to review and approve any publication which results from the project.
- 4.2.9.5. Any clinical trial performed with sponsorship of the MCTG will be listed on the NIH clinical trials website (www.clinicaltrials.gov). As such, a report on the results of the trial will be published at its conclusion, even if the trial is stopped early or not completed. The industry sponsor will not have the authority to create a publication of these results, to be submitted for approval of the SC; however, if no such report is created, the SC will have authority to report the outcome of the trial, and to publish this report.

4.3. Performing a Clinical Trial

4.3.1 Essential Components

As part of the process of protocol review, and as a condition of beginning patient enrollment, a number of resources and steps are required, which will be the primary responsibility of the PI. These include assigning the following roles:

4.3.2. Principal Investigator:

As discussed previously, each clinical trial must have a clearly defined PI who is responsible for all phases of the research project. The Committees of the MCTG will offer assistance and provide oversight during performance of the trial as needed.

4.3.3. Director of Research Operations:

As outlined in section 2.5.1., a Director of Research Operations (DROP) who will serve as the primary interface between the SC and the PI (this may be an employee of a third-party contracted organization, such as the DCC at UC-Davis) Depending on the organization and funding of the trial, the DROP may perform only monitoring functions, or may assist the PI in organizing and running the trial, including coordinating data collection, training and supervising site investigators and coordinators, and performing monitoring visits to participating sites. The DROP will report to the Chair of the SC.

4.3.4. Study Coordinator(s):

Each clinical trial will require one or more study coordinators to work with the PI in performing the clinical trial. Coordinators are usually based at participating institutions, and perform subject enrollment, data collection, and other day-to-day functions of the project. Coordinators may have full- or part-time responsibilities for a specific trial, and be paid entirely or in part by the study grant, if funding is available. Study coordinators may be employees of an appropriate third-party, such as the DCC at UC-Davis.

4.3.5. Site Investigators:

For multicenter studies, each participating institution must identify a site principal investigator (SI) who will be responsible for performing the trial at his/her institution. SI's should be physicians who direct clinical care of patients in the trial. Each site should also provide a study coordinator to work with the SI in performing the trial. It will be the responsibility of the Project PI to identify and appoint SI's, and each SI will be responsible for recruiting one or more study coordinators. The SI will be responsible for performing the trial in an ethical manner and in accordance with study protocols. The DRO will be available to orient and train SI's and study coordinators, and to follow the progress of the trial as it proceeds. The Steering Committee will approve site investigators appointed by the PI. Site investigators must adhere to regulations set forth by their institution, as well as MCTG and other agency regulations.

4.3.6. Data Coordinating Center (DCC)

For every trial, consideration should be given to centralized collection and storage of data. In many circumstances this will involve creating or contracting with a DCC which has expertise in computerized data entry, statistical analysis, and other components of study design. In other cases the resources of the host institution for the trial may be sufficient for data management. The mechanism for data collection should be clearly stipulated and described in the study protocol.

4.3.6.1. Identification of the DCC: The Steering Committee will assist the PI in identifying and authorizing a DCC for the performance of each trial. The MCTG may maintain relationships with one or more certified DCC's for this purpose, and they will be employed on a contractual basis, through the ABA Central Office, as needed. The Data Management and Analysis Committee will participate in identification of data parameters to be collected in the trial, design of data collection forms, proscribed methods for analysis of study data, and design of a strategy for randomization and blinding of results. The responsibility for recording data will be specified in advance as exclusively or partly that of the DCC, the PI, the DMAC, or a combination to be clearly specified in the study protocol.

4.3.6.2. Available Resources: The DCC must be able to provide all of the following:

1. A Director who is responsible for all functions of the DCC.

2. One or more biostatisticians who are available to help with study design and data analysis as needed.
3. Facilities and personnel for secure and permanent data entry and storage, including appropriate backup and security, sufficient data servers and computer access, and the ability to create and use web-based data entry by participants.
4. Willingness to work with the DRO and SC.

4.3.6.3. Budget and Contractual Issues: Many DCC's are independent facilities functioning within University Medical Centers. The DCC for a particular trial will be selected by the PI, and approved by the SC. The DCC must submit a budget for performing the trial which will be approved by the SC. Accountability for executing the MCTG's responsibilities in this contract rest with the Chair of the SC and ultimately with the American Burn Association.

4.3.6.4. Ongoing Data Analysis: An important part of any clinical trial is the ability to evaluate data collection in real time. The DCC must be able to maintain confidentiality of data, but also be prepared to provide a full analysis of data, including any randomization scheme, to the DSMB when requested. Periodic planned reviews of data should be part of the study protocol; unplanned "emergency" reviews may also be necessary. The DCC must be able to cooperate with either circumstance.

4.3.7. Data Safety Monitoring Board (DSMB).

Any project involving interventions in patients must have a DSMB to provide independent oversight and review.

The DSMB will be created with the assistance of the PI, the Quality Assurance, Safety and Regulatory Committee, and the Data Management and Analysis Committee. However, it must be emphasized that the DSMB is an independent body, excluding members who are involved in the study, potential participants or co-authors, or who are employees of the ABA, the Steering Committee, or other MCTG members. The DSMB may be a contracted third-party, which would work in conjunction with a similar committee of the MCTG.

4.3.7.1. Composition: Each interventional study should have a DSMB composed of members specifically selected for the study. There should be at least three members. Typically, at least one member should be an expert in biostatistical methods. Other members should be selected for their expertise in the topics addressed by the trial. Examples might include clinicians, pharmacists, radiologists, pathologists, or others. Lay people including attorneys and clergy may also be appointed when considered appropriate. Contracts for the participation of DSMB members will be negotiated by the ABA, in conjunction with the QASRAC, as needed.

4.3.7.2. Appointment: Unless otherwise addressed contractually with a third-party DSMB, each DSMB will have a Chair, to be appointed by the PI and approved by the SC other relevant Committees. At least two other members will be appointed by the SC as well. However, the Chair of the DSMB will have authority to appoint ad hoc members as needed.

4.3.7.3. Responsibilities of the DSMB: The DSMB is intended to serve as an independent monitoring body to help in assuring that all study subjects receive safe and ethical treatment, that unforeseen complications are detected and evaluated, that methodology is appropriate and adhered to, and that the results of the study are analyzed in a rigorous and objective manner. Accordingly, it is desirable that any contracted third-party DSMB should have authority for all of the following, all of which should be conducted in conjunction with the DSMB committee of the MCTG:

- 1. Review of Adverse Events:** For each study, a mechanism for reporting adverse events (AE's) to study subjects will be specified in the protocol. Investigators are required to submit AE reports to the DSMB, which will review and evaluate them in a timely manner according to the specifications of granting agencies and local IRB's.
- 2. Review and Unblinding of data:** The DSMB may at any time request all of the study data collected to date for review of untoward events, protocol compliance, significant differences in results, or any other purpose. Unblinding of data may be required for this, at the discretion of the DSMB.
- 3. Planned Reviews of Data:** Periodic reviews of data should be planned at the start of the project, and specified in the study protocol. At these reviews, the DSMB will evaluate all data collected so far, and report to the SC any significant results which affect patient safety, efficacy of the intervention, or deviations or problems with the protocol which appear to compromise patient safety, or the validity or statistical rigor of the trial.
- 5. Study conclusion:** At the conclusion of data collection, analysis of the study data will be reviewed by the DSMB. Depending on the protocol, the DSMB may have the authority to approve this data analysis, and its conclusions, or the DSMB may review data analyzed from another source.

Stopping the trial: The DSMB will have authority to stop enrollment into any study in which problems with study design, results of treatment, or significant deviation from protocols are perceived which appear to impact patient safety or interfere with the accuracy or integrity of the protocol.

1. If interim data analysis indicates a clear advantage to the intervention being evaluated.

2. If interim data analysis indicates a clear hazard to the subjects from the intervention being evaluated.
3. If interim data analysis indicates that further subject enrollment is highly unlikely to permit rejection of the null hypothesis.

Exclusion of Centers or Investigators: The DSMB will have authority to recommend disqualifying individual investigators or centers from participating in an ongoing trial if they perceive ethical or protocol violations which appear to compromise subject safety or study accuracy. This will be done by notifying the SC, as described below.

Revision of Protocols: The DSMB will have authority to recommend revisions to clinical protocols if perceived problems or deficiencies are discovered which appear to threaten subject welfare, or to impact the accuracy or feasibility of the study. The DSMB will have the right to approve protocol changes before permitting a study to proceed.

Notification of the Steering Committee: The DSMB will inform the Chair of the SC and the PI of any of the above actions at the time a decision is made to suspend a study, disqualify participants, or revise the protocol. However, approval from neither the Chair of the SC nor the PI will be required for the DSMB's decisions to go into effect.

4.3.8. Trial Performance:

The process of beginning a clinical trial occurs when the study protocol has been approved by all components of the MCTG, the PI has recruited participating centers, budgets have been provided, and participants have been trained by the DROP and PI. Most studies will hold one or more investigators' meetings for these purposes prior to beginning study enrollment. In some cases it may be helpful or necessary for the main study coordinator, the PI, the DROP, or all of these people to visit participating sites to be sure that everything is in place for the safe enrollment of subjects and performance of the trial. The PI and DROP should review each center's facilities, personnel, and commitment to the project, to be sure that the IRB approval and other guarantees of safety are in place, that a DSMB is in place, and that a mechanism exists for reporting AE's to the DSMB. These exigencies should be defined and enumerated as part of the study protocol. In many cases it will be advantageous to begin patient enrollment in one center at a time, bringing all participants on board over a specified period of weeks to months, to be sure each facility has the attention and resources needed to deal with unanticipated problems or questions. (The following specifics are desirable but subject to modification in contracting with a third-party, such as the DCC at UC-Davis, to perform some or all of said functions.

- 4.3.8.1. Inspections/Review:** At the start of each trial, plans should be made for routine review of study progress, patient enrollment, performance, and data collection to be performed by the DROP or Study Coordinator. This may require a visit to the site for this purpose, and this should be included in the

budget. At this visit, the coordinator should be prepared to verify that the protocol is being followed, that safeguards for subject safety are in place, that data is being collected in accordance with the protocol, and that all personnel are familiar with the processes of the study.

As an alternative, the coordinator/DROP may elect to review data submitted electronically or by mail in lieu of a visit to the center. This may be particularly appropriate following an initial site visit at the beginning of the study. In either case, periodic reviews of each center's participation should be planned at the beginning of the study.

- 4.3.8.1. Interim Performance Review:** In addition to periodic reviews of the project by the Coordinator, the DSMB should design periodic reviews of study data and progress. One major purpose of these interim reviews is to determine if subject enrollment is proceeding as planned, particularly since investigators are often overly-optimistic about their ability to enroll subjects; trials are sometimes stopped by the DSMB if subject enrollment is too slow to permit collection of enough data to address the major hypothesis of the trial. In addition, sometimes individual sites fail to keep up with subject enrollment; in that case, it may be necessary to eliminate some site, recruit additional sites, or both.

Interim data analysis is another important component of the interim review. Most clinical trials address the null hypothesis, and estimate the number of subjects required to reject it. If the difference between the control and experimental groups is greater than anticipated, a sufficient difference between groups may be reached unexpectedly early, thus stopping the trial before enrollment is completed. Conversely, if interim analysis reveals little or no differences between groups, the DSMB may conclude that the project is unlikely to be able to refute the null hypothesis because of lack of power, and thus elect to cancel further enrollment. Either of these conclusions would be particularly appropriate if the intervention or its control appears to carry significant risks to patients.

Results of these interim reviews should be presented by the DSMB to the PI and the SC, along with recommendations to continue, modify, or stop the clinical trial.

4.3.9. Concluding the Trial:

At the conclusion of each clinical trial, several steps must be completed.

- 4.3.9.1. Final Data Summation and Analysis:** All data collected during the study must be tabulated, analyzed, and submitted to the PI, the DSMB, the Data Management Committee and through these to the SC. The PI is responsible for assuring that the data is complete, that no significant findings have been omitted or overlooked, and that AE's and complications have been reported accurately. The DSMB must agree with these findings, and state that study enrollment may cease.

- 4.3.9.2. Announcement of cessation of enrollment:** The PI, DROP or study coordinator must contact each participating center and inform them that study

enrollment should stop. Plans for submission of final data, return of unused drugs or materials, and possible participation in a summary investigators' meeting should be planned.

- 4.3.9.3. Publication:** The PI should present the data from the project to the SC, along with plans for preparing an abstract for presentation at an appropriate scientific meeting, as well as a manuscript that reports the results of the study for publication in a peer-reviewed journal, preferably the Journal Of Burn Care & Research. A timetable for this should be agreed on, and the manuscript submitted to the Grants and Publication Committee for review and acceptance before it is submitted for publication.

An important component of this process is agreeing on co-authorship. Inclusion of co-authors should be performed according to published guidelines for this process. This should be agreed upon at the start of the project. The Grants and Publications Committee and ultimately the SC with arbitrate any disagreements regarding this issue. Suggested guidelines are published in the article, "Consensus Statement on Surgery Journal Authorship", *Ann Surg*, 2006;243:713.

As stated previously, only after a manuscript has been approved by the Grants and Publication Committee and the SC should it be submitted for publication. Manuscripts without such approval cannot include any reference to the MCTG or state that the project was conducted by or with the assistance of the MCTG or ABA. This also applies to any abstracts of this work which are submitted at a scientific meeting.

- 4.3.9.4. Notification of Subjects:** In some circumstances investigators may have agreed to inform study subjects of the outcome of the trial, or they may find this advantageous or ethically necessary. This may include informing participants of their randomization status. In such cases the SC and the DSMB must approve this process. Performing this notification is the responsibility of the PI.
- 4.3.9.5. Announcing Study Closure:** In addition to informing investigators, the PI must announce completion of the trial through the MCTG website, and be filing an appropriate announcement with the ClinicalTrials.gov website (<http://www.clinicaltrials.gov/>).

SECTION 5.0: NON-INTERVENTIONAL STUDIES

5.1. Purpose:

Although the major impetus for creation of the MCTG has been to facilitate performance of large-scale randomized controlled clinical trials of interventions in burn treatment, almost all of the research performed to date has been non-interventional; that is, it has not required subjects to be subjected to any therapeutic manipulation, procedure, or drug. Our published studies have consisted primarily of clinical reviews of important conditions in burn treatment, and attempts to define the current status of knowledge or practice within our specialty. As we attempt to move into the "mainstream" of clinical trials research, we recognize the continued value of these non-interventional studies, and the need for the MCTG to support ABA members in performing this research, to educate members in research methodology, and to help in developing and conducting modest research projects.

Because a variety of models for non-interventional studies exist, procedures for each will differ. The following section will present some guidelines for performing retrospective studies, chart reviews, quality assurance and improvement projects, practice guidelines and other non-interventional research.

5.2. Types of Non-Interventional Studies

By definition, a *clinical trial* is a randomized, (usually) blinded study in which a therapeutic maneuver, procedure, or drug is tested in an *experimental group* of subjects, and compared against a *control group* of subjects who are not given this intervention. While clinical trials are considered the "gold standard" for testing therapies in clinical settings, this format is not applicable to every research question. A variety of valuable clinical research models can be utilized to answer questions or develop information outside of the clinical trials setting. Some common types include:

5.2.1. Prospective Non-Randomized Studies:

Like clinical trials, this type of study is prospective; that is, it enrolls subjects as they are admitted for care, and follows them through their course of treatment. Unlike a clinical trial, however, subjects are not randomized to receive different types of treatment. Instead, subjects are given standard treatment, and followed to determine their outcomes. This type of prospective observational study has the potential advantage over retrospective studies of enrolling all subjects with a given condition, so that results are not as subject to selection bias. As an example, all patients with inhalation injuries could be identified on admission, and followed for one year to determine their outcomes. Prospective studies are more expensive than retrospective studies, because they require a research coordinator to identify and enroll patients on admission. This almost always requires IRB approval and a consent document. Another disadvantage to any prospective study is that it depends on subject accrual; investigators are notoriously likely to over-estimate this process, leading to excessively optimistic projections of the speed of completion of the study. Many studies have failed because of inadequate enrollment. This component should be reviewed by the PI, and the Protocol Design Committee. Methodology for following patients, and estimations of drop-out rates, should also be included.

5.2.2. Case-Control Studies:

A case-controlled study is a type of non-randomized study in which a group of subjects is compared to another group separated by time, by center, or other factors. For example, a common study is to compare patients treated over two consecutive time periods, to determine the effect of a designated change in treatment on patient outcome. Case-controlled studies can be prospective in nature, though most are either entirely retrospective, or require a retrospective "control" group of patients. The weakness of these types of studies is that they presume that only defined variables differ between groups, a contingency which cannot be assured without randomization. However, they can often be performed relatively quickly, and with limited budgets. Protocols for such studies should include consideration of comparison of groups for independent variables that could influence outcome, such as age, sex, and burn size.

5.2.3. Retrospective Clinical Review:

This study utilizes data on patients who have already been treated, and summarizes key components of their care (also called a "chart review" project). While this type of project can contain inherent biases, including treatment differences not readily detected or explained, it permits a large number of patients to be reviewed relatively quickly, particularly if multiple centers contribute data. The MCTG's reviews of patients with Toxic Epidermal Necrolysis (TEN) and purpura fulminans are examples of this type of study. Retrospective reviews require much fewer resources than prospective trials, but usually require IRB approval. Methods for data collection, including clear inclusion/exclusion criteria, definition of key terms, and statistical methods to be used, should be stipulated in the protocol.

5.2.4. 'Data Mining' Exercise:

This type of project is a variation on a retrospective review. Typically these projects utilize large computerized multi-center patient registries such as the National Trauma Data Bank (NTDB), National Burn Repository (NBR) and others. Strengths of this type of study include the fact that data may be available for thousands of patients, which tends to dilute out any biases from individual centers or patients. In addition, since data points have already been collected, this type of project consists almost entirely of computerized data analysis; as such, it is inexpensive to perform. A protocol for such an exercise must include how access to databases are to be obtained, and the personnel and resources available for data and statistical analyses, which may be fairly sophisticated. This type of exploratory study can be viewed as a pilot study that allows definition of a clinical problem to be later studied in a more rigorous fashion.

5.2.5. Case Report and Case Series:

A case report is, as implied, simply a report of a remarkable or unusual case. A case series is a collection of a number of such reports, often with a review of the literature. A simple case report can be performed entirely without the approval of the MCTG, though the group would be happy to assist investigators who have questions about proceeding with this type of publication. When multiple cases of the same clinical condition are

combined, the case series can resemble a retrospective clinical review; in fact, review of a single interesting case can stimulate a larger review of patients. Remember that case reports and case series now usually require IRB approval as well as protection of patient identity. In those circumstances patient consent will be required.

5.2.6. Clinical Practice Guideline:

Practice Guidelines have become popular in the past 15 years as a way of summarizing current knowledge and accepted practice for a host of medical conditions. The ABA developed a set of Practice Guidelines for acute burn care in 2001 (*J Burn Care Rehabil*, 2001; suppl); subsequent guidelines have been added and updated since.

Practice guidelines (PG's) should adhere to a set of defined rules regarding levels of evidence, and strength of recommendations. Formulation of PG's requires a meeting of experts, and a review of available literature. The ABA's Committee on Organization and Delivery of Burn Care (CODBC) has assumed responsibility for the ABA's "official" PG's. Investigators are encouraged to contact the CODBC Chair for more information.

Anyone requesting financial support for creation of PG's must submit a concept proposal as outlined above. Should the CODBC initiate a request for PG's, those concept proposals must also pass through the pathways outlined above.

5.2.7. Consensus Conference:

The consensus conference is another way to determine the current attitude or knowledge regarding a particular clinical problem. These are ordinarily organized as a one- or two-day meeting attended by a number of experts, each of whom reviews a particular aspect of care. The ABA's "State of the Science" conference (*J Burn Care Rehabil*, 2007;28, number 4) is an example of a Consensus Conference.

Funding of consensus conferences would not ordinarily be considered part of the mission of the MCTG. Other funding sources are available through the Agency for Health Research and Quality, and the ABA. However, the MCTG might be available to help plan a conference, or create a proposal for funding. This would also require a concept proposal through the Grants and Publications Committee.

5.3. Performing a Non-interventional Study

5.3.1. Basic Components:

Although the methodology for the performance of non-interventional studies is less formal and rigorous than that outlined above for clinical trials, the framework of the process should still be followed for any study conducted through, or with assistance of, the MCTG. This includes compliance with all regulatory and ethical policies, the regulations and oversight of the MCTG Steering Committee, and use of committee structure for protocol development.

Some simple studies will not require financial support or access to a DCC, the DRO, a DSMB, or other resources supported by the MCTG. Investigators have the option to perform some or all of these functions themselves. However, for any MCTG-supported

project a formal protocol must be created which includes the essential components outlined below. This protocol must be approved by the SC before the research is performed if it is to be considered or stated to be an MCTG-sponsored project.

5.3.2. Research Protocol Development

Development of a proposal to conduct a non-interventional research project should follow the process outlined in Figure 4.1, though not all steps will be required. It should proceed as follows:

- 5.3.2.1.: Principal Investigator:** As outlined previously, each project must have a clearly-identified PI who is responsible for the performance of the project. While multiple investigators or participants may be needed to perform the project, one individual must be primarily involved in interactions with the MCTG, and bear responsibility for the performance and results of the project.
- 5.3.2.2. Concept Proposal:** The investigator should submit a brief proposal outlining the concept of the study to be performed to the Non-Interventional Studies Committee (NISC). A sample form for this is contained in the appendix. This proposal should state the hypothesis to be tested, or anticipated results to be achieved by the project. It should include a description of the methodology proposed, the length of the project, whether it will be a multicenter project, and an estimation of the resources required to complete the project. This proposal need not be more than three pages in length; inexperienced investigators who are requesting the assistance of the NISC need only submit a rough outline of the concept.
- 5.3.2.3. NISC and Steering Committee Review:** The NISC will review all concept proposals submitted by members within a period of 15 business days. The proposal and the NISC's recommendation will then be forwarded to the SC, who will classify the proposal into one of three categories:
- Reject:** The proposal does not address a problem of significant importance, or is ethically or practically unfeasible, or requires resources which are not available. Proposals which are rejected will not be considered further. However, it should be emphasized that a stated goal of the MCTG is to encourage the performance of clinical research by ABA members, many of whom may have little research experience. Therefore, every attempt will be made to work with the investigators to produce a proposal that is important, ethical, feasible and practical.
- Revise/Resubmit:** A proposal which appears to have some merit, but includes some components which must be clarified or corrected before it can be considered acceptable, will be returned to the author for revision, and resubmission to the NISC.
- Accept:** A proposal which is accepted will be submitted to for full review by the appropriate Committees of the MCTG.

This decision will be announced by the SC not more than 15 business days following receipt of the NISC report. The vote of a simple majority of SC members will be required for any action.

The NISC's findings will be submitted as a report to the author of the proposal.

- 5.3.2.4. Creation of a Formal Protocol:** Following acceptance of a concept proposal, investigators will be encouraged to develop a formal protocol for performance of their research project. The resources of the MCTG will be made available to investigators who request them, though it is recognized that some projects will require little or no evaluation of budget, ethics, data management, etc. Depending on the nature of the project and the degree of development of the concept proposal, the SC will direct investigators to submit their protocol for review to appropriate committees as needed. Any investigator who is applying to the MCTG for financial support, including use of the DCC, the DRO, web-based data entry development, or support for travel or meetings, must submit their protocol through the formal process outlined in Figure 4.1.

The resources of the MCTG will be made available to ABA members on request. It should be emphasized that any investigator who requests help with protocol development from any Committee of the MCTG will receive it, even if the SC does not direct the investigator to submit his or her proposal through that Committee. The SC will determine the priority and order of attention to submitted proposals, based on perceived importance of the project, the resources available to perform it, and the work loads of the respective Committees.

- 5.3.2.5. The Research Protocol:** Although many non-interventional studies will not require as formal or detailed a protocol as a clinical trial, the protocol should contain the same essential components. These include:
- Background:** A statement of the experience or data supporting definition of the clinical problem to be addressed.
 - Hypothesis/Aims:** The question to be tested by the proposed project, or the desired results of the project.
 - Methodology:** A brief description of how the project will be performed. This should include the number of participating sites, resources to be accessed, data to be collected, who will collect it, how it will be stored and analyzed, and the anticipated means of publishing the data. The need for IRB approval, inclusion/exclusion criteria, anticipated length of the study, and other details should be included.
 - Budget:** An estimate of the resources required to perform the project.
 - Principal Investigator:** As noted previously a clearly identified PI is essential for any proposed project. The PI will assume primary responsibility for the design, performance, and results of the project.

- 5.3.2.6. Protocol Acceptance and Performance of Research:** Formal protocols for non-interventional studies must be approved by the NISC and the SC before the research is conducted. Once accepted, the investigator will be instructed

to begin the project. If the project requires MCTG resources, the SC will direct the DCC, DROP, and appropriate Committees to assist in performance of the research.

- 5.3.2.7. Reporting and Publishing Results:** Abstracts and manuscripts resulting from the performance of non-interventional research must be submitted to the Grants and Publications Committee as outlined in Section 4. Any document which is stated to be a product of, or produced with assistance by the MCTG must be approved by the SC prior to publication.

5.3.3. Website Posting/No Assistance Required

In some circumstances an investigator may wish to perform a non-interventional study without the assistance of the MCTG, but may wish to use the MCTG website to advertise the study and recruit participants. The MCTG will maintain a section on the website devoted to "studies in progress". Postings on this website will include the nature of the project, the PI, and whether this is an MCTG-sponsored project. Investigators may request posting on the Website without the endorsement or participation of the MCTG. However, this will still require submission of a concept proposal to the Non-Interventional Studies Committee.

SECTION 6-0: GLOSSARY OF TERMS AND ABBREVIATIONS

- 6.1. **ABA:** American Burn Association
- 6.2. **Ad hoc:** literally, "at hand". This usually refers to creation of a committee, or appointment of a member to a committee, for a specific and limited purpose. For example, an expert on medical ethics might be appointed to advise a DSMB on a specific ethical issue. Ad hoc membership is covered in section 3.2.2.3.
- 6.3. **BOT:** Board of Trustees of the American Burn Association.
- 6.4. **CFR:** Code of Federal Regulations. Cited in section 2.1.2.
- 6.5. **Clinical Trial:** This term refers to a specific type of clinical research in which study subjects are randomized to receive either a specific intervention to be tested (the "study group") or to receive either no intervention, or widely-accepted standard care (the "control" group). Many clinical trials are multi-center; that is, they are conducted at more than one hospital or medical center. Clinical trials are ideally performed in a randomized and double-blinded manner, which means that neither caregivers nor subjects are aware which subjects receive the study intervention, and which are controls. Thus clinical trials are often referred to as "randomized controlled trials (RCT's)".
- 6.6. **Coordinators:** Study coordinators are health care professionals, usually nurses, employed to perform clinical trials, record data, and monitor subjects. In performance of an MCTG-sponsored trial, each institution will identify one or more coordinators who will be trained and familiarized with the protocol. The DROP will assist in training coordinators, and monitor their performance during the trial.
- 6.7. **DCC:** Data Coordinating Center. Each trial will create or utilize a center which will collect, store, and analyze data generated during that trial. The ABA is in the process of contracting with a DCC at the University of California Davis. This facility should be available for use by investigators performing MCTG-approved studies. Investigators who obtain outside funding for research projects may utilize another DCC with approval of the Steering Committee.
- 6.8. **DMAC:** Data Management and Analysis Committee. See Section 3.7 for a general description of the Committee and its duties.
- 6.9. **DROP:** Director of Research Operations. See Section 4.3.3 for a description of the position and qualifications for this position.
- 6.10. **DSMB:** Data Safety Monitoring Board. An independent board to provide external review of the safety and efficacy of the trial, which is an essential component of each clinical trial. The DSMB is described in detail in Section 4.3.1.

- 6.11. **FBC:** Feasibility and Budget Committee. See Section 3.5 for a general description of the Committee and its duties.
- 6.12. **GCP:** Good Clinical Practice. Refers to the standards contained in the publication "Guidance for Industry ICH E6: Good Clinical Practice: Consolidated Guidance" US Dept of Health and Human Services, Food and Drug Administration, April, 1996. Available at www.fda.gov/oc/gcp/guidance/html.
- 6.13. **GPC:** Grants and Publications Committee. See Section 3.3. for a general description of the Committee and its duties.
- 6.14. **ICH:** International Committee on Harmonization. Cited in Section 2.1.2.
- 6.15. **IRB:** Institutional Review Board: Every academic medical center maintains an IRB for the purpose of ensuring the rights and safety of human study subjects, adherence to all guidelines for the ethical performance of research, and compliance with federal and other regulations regarding research performance. Clinical trials conducted at health care facilities will be monitored by local IRB's; investigators will be required to obtain IRB approval and comply with local IRB regulations and oversight of all study procedures.
- 6.16. **MCTG:** Multicenter Trials Group of the American Burn Association.
- 6.17. **NISC:** Non-Interventional Studies Committee. See Section 3.8 for a general description of the Committee and its duties.
- 6.18. **PDRC:** Protocol Design and Review Committee. See Section 3.4. for a general description of the Committee and its duties.
- 6.19. **PI:** Principal Investigator: Each study conducted through the MCTG must have one or more clearly identified Principal Investigators, who will be responsible for the creation, conducting, analyzing, and reporting of the study results. Each Principal Investigator will be required to enter into an agreement with the MCTG to adhere to the group's policies and procedures, conduct research in an ethical manner consistent with good clinical practice, and to report their findings to the SC.
- 6.20. **Power Analysis:** Power analysis is a calculation intended to determine the size of a study sample required to provide enough data to reject the null hypothesis. Many clinical trials have had insufficient sample size, making it impossible to conclude whether there was no real difference between treatment strategies, or simply that more patients would have been needed to conclude this with confidence. Performance of power analysis should be performed by the PI in constructing a protocol, and confirmed by the DSMB. Power analysis requires some estimations of the magnitude of the difference expected between treatment and control groups, and a decision regarding the level of assurance that this difference can be detected.
- 6.21. **QASRAC:** Quality Assurance, Safety, and Regulatory Affairs Committee. See Section 3.6 for a general description of the Committee and its duties.

- 6.22. **Protocol:** A study protocol is a detailed outline of the procedures to be followed during performance of the clinical trial, or other clinical research. A protocol for each study must be developed and approved by the SC before the study can begin; adherence to the protocol will be monitored throughout the performance of the study, and deviations from the protocol will be noted by the DROP, the DCC, and the DSMB. Failure to adhere to an approved protocol may invalidate the results of the study, lead to withdrawal of MCTG support, or disqualification of a specific investigator(s).
- 6.23. **SC:** Steering Committee of the Multicenter Trials Group. See Section 3.1 for a general description of the Committee and its duties.

SECTION 7

American Burn Association Multi-Center Trials Group Bylaws

Adopted by the Board of Trustees, April, 2007

I. Name and Structure

- A. The organization shall be known as the American Burn Association — Multicenter Trials Group (ABA-MCTG)
- B. The ABA-MCTG is an affiliate organization of the American Burn Association. The ABA-MCTG shall have the mission, structure, membership, and other organizational and operational components as set forth in these bylaws, as approved by the ABA-MCTG Steering Committee and the ABA Board of Trustees, and as may be amended from time to time and approved by same.
- C. The ABA-MCTG will operate under the oversight of the ABA Board of Trustees and provide reports, at the Interim and Annual ABA Board of Trustees Meetings, describing the peer review process and other matters related to protocol design, research-agenda setting, quality assurance, patient safety, grant applications and awards, multi-center trials in process or planned, and such other matters as the ABA Board of Trustees may request.

II. Purpose

- A. Mission Statement
The American Burn Association Multicenter Trials Group is dedicated to optimizing the outcomes of care for burn injuries through multi-center evidence-based research. The ABA-MCTG will provide the leadership, education and infrastructure needed to facilitate research collaboration and information exchange among researchers, burn care providers, and the communities they serve.
- B. Research Agenda
The research agenda of ABA-MCTG will be focused on achieving the goals of the mission statement. In general, however, the research agenda will follow that of pre-existing consensus-derived research agendas of the American Burn Association (ABA).

III. Committee Structure

- A. ABA-MCTG Steering Committee and Other Committees
 1. ABA-MCTG Steering Committee
 2. Protocol design and review Committee
 3. Feasibility and budget Committee(accounting, clinical coordination, statistical)
 4. Data management and analysis Committee
 5. Quality assurance, safety and regulatory Committee
 6. Grant/Publication Committee
 7. Data Safety Monitoring Board (DSMB)
A DSMB will be formed as needed for individual studies. It will operate independently of, but report to, the Steering Committee.
 8. Data Management and Coordinating Center (DMCC)

9. Working Groups
10. Individual Study Lead Centers (ISLC)
11. Burn Center Affiliates (BCA)

IV. ABA-MCTG Membership

- A. Network Membership
 1. Active members are defined as individuals who are participating within the structure of ABA-MCTG as set out under section III.
 2. In addition, members of the Board of Trustees, as well as the Executive Director and Associate Executive Director of the American Burn Association will be considered Active members.
- B. Steering Committee and Other Committee Membership

Only active members of ABA-MCTG may serve as members of the ABAMCTG Steering Committee and chair other Committees.

 1. Steering Committee

The voting members of the Steering Committee will consist of 7 members. No more than five members can be physicians.
 2. Other Committees

The chair of each Committee will be selected by the Steering Committee. Each Committee chair will appoint additional members essential for functioning of the committee subject to approval of the Steering Committee. All Committee members have voting privileges within the Committee.

V. Officers of the ABA-MCTG

- A. Steering Committee
 1. Steering Committee Officers

Officers of ABA-MCTG Steering Committee will include the Chair, Vice-Chair, Treasurer, and Secretary. All officers will be voted into office by the steering committee.
 2. Duties of the ABA-MCTG Steering Committee officers:
 - a. Duties of the ABA-MCTG Steering Committee Chair are primarily those of overseeing the operation of ABA-MCTG, including coordinating and running the Steering Committee meetings, and, maintaining ongoing communications with all other entities, including the ABA Board of Trustees
 - b. Duties of the Vice-Chair include assisting the Chair with ABA-MCTG responsibilities, as deemed necessary. The Vice-Chair may officiate at meetings in the temporary absence of the Chair. If the Chair becomes unable to perform his/her duties as determined by a majority of Steering Committee members, the Vice-Chair will assume the Chair's responsibilities and will initiate a vote by the Steering Committee to select a new Chair.
 - c. The ABA-MCTG Secretary will be responsible to ensure that careful and authentic records of Steering Committee proceedings are kept. These duties will include carefully reviewing Steering Committee minutes and summaries for their accuracy and integrity. The Secretary will also maintain an updated list of all committee officers and members and ensure that a copy of the ABA-MCTG bylaws is available at all Steering

Committee meetings. The Secretary will be responsible for posting and/or publishing Steering Committee minutes and communications to the American Burn Association and the ABA-MCTG website, as directed by the committee.

- d. The ABA-MCTG Treasurer will be responsible for managing any and all financial dealings of the ABA-MCTG in cooperation with the ABA Board of Trustees.
- B. Officers of Other Committees
1. Committees will be led by a Chairperson.
The duties of these Chairs will be to oversee the operation of their Committees as directed by the ABA-MCTG Steering Committee. This includes appointment of Committee members. These Chairs will report to the ABAMCTG Steering Committee.
- C. Terms of Office, Qualifications, and Elections
1. Terms of Office
 - a. Steering Committee officers will be elected by the voting members of ABA-MCTG and their initial terms shall be as agreed to by the officers but not to exceed five years. Subsequent terms of officers will be for five-year terms and be staggered so that no more than two officers are elected each year, ensuring continuity of leadership.
 - b. All other committee members serve 5-year terms.
 2. Qualifications
 - a. The Steering Committee Chair must be a member of the ABA, and have previously served on the Steering Committee. He/she must have a MD or PhD and be actively participating in clinical burn research.
 - b. The Committee Chairs of other Committees must be members of the ABA-MCTG and if they are not a member of the Steering Committee, they and will attend Steering Committee meetings by invitation only.
 3. Elections
Steering committee members will be elected by ballot vote on the ABAMCTG website or at the ABA Annual Meeting. The Steering Committee will nominate at least one person for each available position on the steering committee and nominations will be received from the ABA-MCTG membership. Winning candidates will be those who receive the most votes.
 4. Chairs of Other Committees
Chairs of other Committees are appointed by the Steering Committee Chair and must be ratified by at least four out of seven members of the Steering Committee.
 5. ABA-MCTG Steering Committee members, officers, and other Committee Chairs can be removed from office by majority vote of the Steering Committee.

VI. Meetings

- A. Frequency of meetings
1. ABA-MCTG Membership
The ABA-MCTG group will meet at least annually at the American Burn Association Annual Meeting.
 2. Steering Committee

Steering Committee meetings will be held at least annually and additionally as deemed necessary. It is the duty of the Steering Committee Chair to call meetings but a meeting can be called by a majority vote of Steering Committee members. There will also be provisions for electronic meetings, as necessary.

3. Other Committees

Committee meetings will meet at the direction of the Committee Chair. Reports from the Committees will be made to the Steering Committee at least annually.

B. Alternates

Alternates for Steering Committee and other Committee members who cannot attend a specified Steering Committee or other Committee meeting must be designated by the committee member and approved by either the Chair or Vice-Chair of the Steering Committee.

C. Voting

1. Membership voting

Decisions are made by majority vote of those votes cast, one vote per member, with two-thirds vote required under special conditions as determined by the ABA-MCTG-Steering Committee (per ABA-MCTG bylaw guidance and Robert's Rules of Order).

2. Committee voting

Decisions are made by majority vote of those votes cast, one vote per member or alternate, with two-thirds vote required under special conditions as determined by the ABA-MCTG-Steering Committee (per ABAMCTG bylaw guidance and Robert's Rules of Order).

D. Quorum

1. Steering Committee

Steering Committee quorum consists of at least five members or alternates.

2. Other Committees

Committee quorum is defined as a majority of those members who attend Committee meetings, either in person or electronically. The Committee Chair or alternate must be present.

E. Robert's Rules of Order, Meeting Confidentiality, and Open Meetings

1. Robert's Rules of Order will be used to conduct all ABA-MCTG meetings.
2. ABA-MCTG Steering Committee and Other Committee meetings are open to all, unless the Committee decides by majority vote to keep a meeting closed.

VII. Committees

A. Standing Committees

1. There are six Standing Committees.
 - a. ABA-MCTG Steering Committee
 - b. Protocol design and review Committee
 - c. Feasibility and budget Committee (accounting, clinical coordination, statistical)
 - d. Data management and analysis Committee
 - e. Quality assurance, safety and regulatory Committee
 - f. Grant/Publication Committee

B. Duties

The descriptions and duties of the Standing Committees are described in the Policies and Procedures manual.

C. Ad hoc committees

The Standing Committees may establish ad hoc committees as necessary to carry out the work of the organization.

VIII. Policies and Procedures

- A. The ABA-MCTG Policies and Procedures manual is a separate document from the ABA-MCTG Bylaws. The Policies and Procedures manual contains the descriptions and duties of the ABA-MCTG Standing Committees, as delineated by the Steering Committee and with its approval. The Policies and Procedures manual will be maintained on the ABA-MCTG website (abaresearch.org).

IX. Code of Ethics

All ABA-MCTG members will be held to the highest ethical principles and standards consistent with the Federal Regulation for Protection of Human Subjects (HRSA Circular No. 96.05, Code of Federal Regulations Title 45 Part 46 [45 CFR Part 46], and the Belmont Report). This includes, but is not limited to, compliance with any and all federal, state or institutional regulations regarding the performance of research.

X. Conflicts of Interest

- A. All ABA-MCTG members are subject to the conflicts of interest policies of their respective educational institutions' policies and applicable federal laws and regulations (per 42 CFR Ch. 1, Subpart F, 50.6), state laws and regulations, and local institutional policies. Potential conflicts of interest are situations which might not allow for impartial or objective determinations. These situations include, but are not limited to, relationships with products, devices, government or companies such as pharmaceutical, formula, or equipment manufacturers. This would also include the receipt of research support or lecture honoraria from such companies or organizations.
- B. In addition to the mandated requirements listed above ABA-MCTG members having any real, perceived or potential conflicts of interest in the development and testing of any drug, technique, methodology or technology are also required to disclose these conflicts to the ABA-MCTG Steering Committee at the time the conflict is recognized. These conflicts will be reviewed by the Steering Committee, which may deem it necessary to limit the role of the member in specific research endeavors in order to ensure scientific objectivity. Failure to disclose these conflicts of interest as required may result in the loss of the privilege to participate in ABA-MCTG and may be subject to disciplinary action by the ABA.

XI. Bylaw Amendments

- A. Amendment proposal.
Proposed bylaw amendments may be presented to the Steering Committee by any ABA-MCTG member.
- B. Amendment ratification
Amendment of these bylaws will consist of providing written notification of

proposed amendments on the ABA-MCTG website and announced at least one year in advance at the ABA-MCTG meeting conducted at the ABA Annual Meeting. The amendment will be ratified by a majority vote of ABA-MCTG members conducted via the ABA-MCTG website.

XII. Construction and Severability

Applicable Illinois laws are hereby adopted as part of these bylaws. If any provision of these Bylaws is in conflict with any Federal or State of Illinois statute, the statute prevails. If parts of the Bylaws are judged illegal, the remainder survives.

Adopted by the ABA-MCTG Steering Committee _____, 2007.

Adopted by the ABA Board of Trustees _____, 2007

SECTION 8

**SAMPLE JOB DESCRIPTION FOR DIRECTOR OF RESEARCH OPERATIONS (DROP)
taken from the Hydrocephalus Research Network**

IICRC Job Title: Director of Data Coordinating Center
Hydrocephalus Research Network (HRN)

% of FTE at IICRC: 100%

Five Major Content Responsibilities

% of IICRC job: 50% **1. Project Direction and Program Management-** Provide direct oversight for all activities relating to the daily operation of the Data Coordinating Center (DCC) including making project assignments and setting dates for completion with staff input. Responsible for managing the development, initiation, conduct, monitoring and completion of clinical studies within the study network (Hydrocephalus Research Network (HRN)). Provide leadership for large, complex protocols within the network. Prepare initial and subsequent IND submissions to FDA, correspond with FDA on study issues, and assure regulatory compliance of the data center. Negotiate budgets, obtain bids, and/or retain services of CROs, central laboratories, drug distribution centers and other vendors for network studies in collaboration with Office of Sponsored Projects (OSP) and the funding agencies. Prepare Informed Consent / Parental Permission / and Assent Form templates for network studies. Responsible for the day to day management of studies within the network and ensuring that these studies are being conducted in accordance with Good Clinical Practices (GCPs), FDA/ HHS Regulations, network and Department SOPs. Oversee development, production and distribution of study related documents (i.e., Manual of Operations, Essential document forms, and training materials). Prepare and track metrics for studies within the network.

Facilitate the collections and submission of supporting documentation for adverse events to the Data Safety and Monitoring Board (DSMB) and Steering Committee. Organize and facilitate event adjudication review and services for clinical research studies. Maintain frequent discussions and email correspondence with staff about progress of various projects, clarification of project goals, problems encountered and refinement of due dates. Provide preplanning for and conducting of weekly DCC meetings. Work with Principal Investigator to develop and revise the DCC budget as needed. Oversee IRB applications/renewals and correspond with IRB on study issues. Work with data manager to develop functional database systems. Promote HRN via website, newsletter, and lectures as desired by the Steering Committee. Communicate with funding officials including provision of progress reports, conference planning, grant guidance review, and attend funding meetings as required. Meet with the project PI monthly to discuss overall direction of program.

% of IICRC job: 25%

2. Staff Supervision - Directly supervise DCC staff members. Support staff in decision making, project planning, and goal setting. Complete evaluations and promote staff development. Provide education, guidance and supervise daily activities.

% of IICRC job: 10%

3. HRN site support – Provide technical and project assistance to HRN site research coordinators, and investigators by telephone, email, site visits and conferences, to aid and solve problems during implementation of study protocols, IRB submissions, data analysis, training programs, protocol compliance, regulatory compliance, data quality, research design, training and site monitoring. Act as a liaison between network personnel.

% of IICRC job: 5%

4. HRN Support: Attend required national meetings, participate in subcommittee activities, planning meetings, present DCC educational lectures, conduct training sessions, and assist with policy development.

% of IICRC job: 5%

5. Continuing Education: Review literature, news and updates regarding pertinent issues in the field (regulatory guidelines, current events, clinical care etc). Attend GCP and clinical trials conferences and educational seminars.

Lesser Content Responsibilities

% of IICRC job: 5%

Administrative tasks (email, KRONOS, evaluations, IICRC meetings, paperwork, etc.)

AMERICAN BURN ASSOCIATION MULTICENTER TRIALS GROUP

CONCEPT PROPOSAL FOR CLINICAL RESEARCH PROJECT

1. Proposal is for: Multicenter Randomized Clinical Trial
 Non-Interventional Research Project

2. Name and Address of Principal Investigator:

Name:

Mailing Address:

Telephone:

Fax Number:

e-mail Address:

Is Principal Investigator a member of the ABA? YES NO

3. Title and brief description of the proposed project:

4. Proposed Site(s) for Performance of the Project (indicate if multiple centers):

5. Estimation of the number of subjects required or available for this project:

6. Estimated time needed to complete the project:

6. Will this project require financial support? YES NO

7. Has support been obtained? YES NO

8. Estimated amount of support needed to perform this project:

9. What is the (proposed) source of support?

10. What support from the Multicenter Trials Group are you requesting? (check all that apply)

- Assistance with designing and writing a protocol
- Assistance in writing a grant for funding
- Assistance in recruiting multiple centers for participation, or in recruiting coordinators
- Assistance in training site investigators and/or coordinators
- Assistance in performing chart review, data mining, or other non-randomized data collection
- Assistance in performing a randomized, interventional clinical trial
- Assistance in data storage and analysis, including statistics
- Assistance in writing and preparing an abstract or paper for presentation/publication
- Assistance with funding for the project

11. On an attached document, briefly describe the following:

- A. Background: What previous research or experience makes this an interesting question to investigate? What previous research has been performed on this topic?
- B. Hypothesis: What question will this project attempt to answer?
- C. Methodology: How will this project be performed? What resources will be needed to complete it?
- D. Budget: If funding will be needed, indicate how much and for what it is needed.

I have reviewed the Policies and Procedures of the American Burn Association's Multicenter Trials Group, and agree to abide by them. In the event that this project is performed with the assistance of approval of the MCTG, I recognize the authority of the MCTG to perform and/or monitor the project. I accept that sponsorship of the MCTG is subject to my conforming to the regulations specified in the policies and procedures.

Signed; _____ Date: _____

This document can be submitted to any member of the Steering Committee of the MCTG, or to:

Jeffrey R. Saffle, MD, FACS
Professor, Surgery
University of Utah Health Center
50 N. Medical Drive
Salt Lake City, UT, 84132
<< Jeffrey.saffle@hsc.utah.edu >>