



THOMAS L. GARTHWAITE, M.D.
Director and Chief Medical Officer

FRED LEAF
Chief Operating Officer

COUNTY OF LOS ANGELES
DEPARTMENT OF HEALTH SERVICES
313 N. Figueroa, Los Angeles, CA 90012
(213) 240-8101

Part
BOARD OF SUPERVISORS

Gloria Molina
First District

Yvonne Brathwaite Burke
Second District

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Michael D. Antonovich
Fifth District

December 2, 2004

The Honorable Board of Supervisors
County of Los Angeles
383 Kenneth Hahn Hall of Administration
500 West Temple Street
Los Angeles, CA 90012

Dear Supervisors:

**APPROVAL OF FIELD ADMINISTRATION OF STROKE THERAPY -
MAGNESIUM TRIAL STUDY MEMORANDUM OF UNDERSTANDING**
(All Districts) (3 Votes)

IT IS RECOMMENDED THAT YOUR BOARD:

1. Approve and instruct the Director of Health Services, or his designee, to sign a Memorandum of Understanding, substantially similar to Exhibit I, with The Regents of the University of California on behalf of the University of California at Los Angeles, primary recipient of Grant Award No. 1 U01 NS044364-01A1 from the Department of Health and Human Services National Institutes of Health, to conduct the Field Administration of Stroke Therapy - Magnesium Trial study, effective upon the date of Board approval through June 30, 2007, with no net cost to the County.
2. Delegate authority to the Director of Health Services, or his designee, to sign any subsequent amendments to this Memorandum of Understanding to accept funds, on substantially similar terms, upon review and approval by County Counsel and subsequent notification to the Board of Supervisors.

PURPOSE/JUSTIFICATION OF THE RECOMMENDED ACTIONS:

This Memorandum of Understanding (MOU) formally establishes the roles, responsibilities, and cooperative status between The Regents of the University of California on behalf of the University of California at Los Angeles (UCLA) and the Department of Health Services (DHS or Department) Emergency Medical Services (EMS) Agency in conducting and participating in the federally-funded Field Administration of Stroke Therapy - Magnesium Trial (FAST-MAG) Trial study whose purpose is to evaluate the efficacy and safety of intravenous magnesium sulfate initiated by paramedics in the field within two (2) hours of symptom onset in patients with acute stroke.

DHS is also seeking delegated authority to enter into subsequent amendments, with substantially similar terms, to accept funding from UCLA for continued participation of EMS in the FAST-MAG Trial study.

FISCAL IMPACT/FINANCING:

UCLA is the prime recipient of the grant from the Department of Health and Human Services National Institutes of Health. DHS will not incur any additional costs associated with their participation in the FAST-MAG trial study.

FACTS AND PROVISIONS/LEGAL REQUIREMENTS:

The County, through its DHS EMS Agency, is authorized to approve or conduct research under California Health and Safety Code Section 1797.221 which states, "The medical director of the local EMS agency may approve or conduct any scientific or trial study of the efficacy of the prehospital emergency use of any drug, device or treatment procedure within the local EMS system, utilizing any level of prehospital emergency medical care personnel. The study shall be consistent with any requirements established by the authority for scientific or trial studies conducted within the prehospital emergency medical care system and where applicable, with Article 5 (commencing with Section 111550) of Chapter 6 of Part 5 of Division 104".

A paramedic may perform any prehospital emergency medical care treatment procedure(s) or administer any medication(s) on a trial basis when approved by the medical director of the local EMS agency. This authority is granted by the California Code of Regulations, Title 22, Division 9, Section 100146.

On September 22, 2003, UCLA was awarded a \$15.3 million grant from the Department of Health and Human Services National Institutes of Health for the FAST-MAG Trial study project. The grant will fund the FAST-MAG project through June 30, 2007. The primary objective of the FAST-MAG Trial study is to determine if prehospital treatment with magnesium sulfate administered by paramedics in the field improves the long-term functional outcome of hyperacute stroke patients.

FAST-MAG Trial study subjects will include 1,298 patients with acute stroke to be identified in the field by licensed and accredited paramedics in Los Angeles County. Paramedics will screen all prehospital emergency medical care patients for study entry. Inclusion and exclusion criteria for study participation have been established in the FAST-MAG Clinical Trial Protocol developed by UCLA. Inclusion of study participants is approved by an on-call FAST-MAG physician-investigator, and written consent by the patient or the patient's authorized representative. UCLA staff will also oversee continued administration of the study at participating 9-1-1 receiving hospitals upon patient arrival.

UCLA will provide training in FAST-MAG Trial study procedures and human subject protection to EMS Agency personnel and EMS prehospital emergency medical care providers at no charge to the County.

EMS Agency will administer this program on behalf of the County.

Under the termination provisions of the MOU, the MOU may be terminated with or without cause with 60 calendar days advance written notice by either party.

Attachment A provides additional information.

Exhibit I has been approved as to use and form by County Counsel.

CONTRACTING PROCESS:

It is not appropriate to advertise this MOU on the Office of Small Business' Countywide Web Site.

IMPACT ON CURRENT SERVICES (OR PROJECTS):

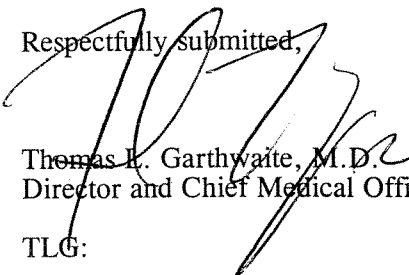
Approval of this MOU will enable the Department to conduct and participate in the FAST-MAG Trial

The Honorable Board of Supervisors
December 2, 2004
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study in cooperation with UCLA to evaluate the potential efficacy of intravenous magnesium sulfate administered by paramedics in the field to patients with acute stroke.

When approved, this Department requires three signed copies of the Board's action.

Respectfully submitted,



Thomas K. Garthwaite, M.D.
Director and Chief Medical Officer

TLG:

Attachments (2)

c: Chief Administrative Officer
County Counsel
Executive Officer, Board of Supervisors
Auditor-Controller
Chair, Emergency Medical Services Commission
Health Care Association of Southern California
Chief, County Health Services Branch
State Department of Health Services

BLETC3591.PPS

SUMMARY OF MEMORANDUM OF UNDERSTANDING

1. **TYPE OF SERVICE:**

The Memorandum of Understanding (MOU) with UCLA will enable the DHS EMS Agency to conduct and participate in the Field Administration of Stroke Therapy - Magnesium Trial (FAST-MAG) study through June 30, 2007.

2. **CONTRACTOR ADDRESS AND CONTACT PERSON:**

University of California at Los Angeles
Office of Contract and Grant Administration
10920 Wilshire Boulevard, Suite 1200
Los Angeles, California 90024
Attention: Sharon Lam
Telephone: (310) 794-3596

3. **TERM OF MOU:**

Effective upon the date of Board approval through June 30, 2007.

4. **FINANCIAL INFORMATION:**

There is no net County cost. However, UCLA, the primary recipient of Grant No. U01 NS044364-01A1 from the Department of Health and Human Services National Institutes of Health for the FAST-MAG Trial study, may provide funding to the EMS Agency to continue participation in the study. A subsequent amendment to the MOU will be executed for such purpose.

5. **RESPONSIBLE FOR MONITORING:**

Emergency Medical Services Agency.

6. **GEOGRAPHIC AREA SERVED:**

Countywide.

7. **APPROVALS:**

Local EMS Agency:	Carol (Gunter) Meyer, Director
Contract Administration:	Irene E. Riley, Director
County Counsel (approval as to use):	Edward A. Morrissey, Deputy County Counsel

EXHIBIT I
Contract # _____

FIELD ADMINISTRATION OF STROKE THERAPY
MEMORANDUM OF UNDERSTANDING

THIS MEMORANDUM OF UNDERSTANDING is made and entered into
this _____ day of _____, 2004,

by and between the COUNTY OF LOS ANGELES
(hereafter "County"),

and THE REGENTS OF THE UNIVERSITY
OF CALIFORNIA (hereafter
"Contractor").

WHEREAS, pursuant to the authority granted under the
Emergency Medical Services and Prehospital Emergency Medical
Care Personnel Act (Health and Safety Code, Section 1797 et
seq., hereinafter referred to as "Act"), the County of Los
Angeles (hereafter referred to as "County") has designated its
Department of Health Services (hereafter referred to as "DHS")
as the local Emergency Medical Services Agency (hereafter
referred to as "EMS Agency"); and

WHEREAS, under Section 1797.221 of the Act and Title 22,
California Code of Regulations, section 100146, the EMS Agency
has the authority to approve or conduct a scientific or trial
study within the EMS System; and

WHEREAS, Contractor on behalf of the University of
California at Los Angeles (hereafter referred to as "UCLA") is
the prime recipient of a multi-year, approximately \$15.3 million
grant from the Department of Health and Human Services National

Institutes of Health, Grant Number 1 U01 NS 44364, awarded for project entitled "Field Administration of Stroke Therapy - Magnesium Trial" (hereafter "FAST-MAG") to study the efficacy of the prehospital emergency use of magnesium sulfate within the prehospital EMS system; and

WHEREAS, Contractor desires the participation of the EMS Agency for said project; and

WHEREAS, the EMS Agency has the ability, and desires to participate in the performance of work described herein under the terms and conditions hereafter set forth.

NOW THEREFORE, the parties hereto agree as follows:

____1. BASIS AND PURPOSE: The purpose of this Memorandum of Understand (hereafter "MOU") is to define the relationship between the EMS Agency and UCLA, relative to participation in activities which support the FAST-MAG Trial study. The objectives of the FAST-MAG Trial study may be met through the joint efforts of the EMS Agency and UCLA.

____2. TERM: This MOU shall commence on the date of Board approval, with such date reflected on the top of page 1 of the MOU, and shall continue in full force and effect to and including June 30, 2007.

____3. AUTHORITIES: The EMS Agency, through the County's DHS, is authorized to approve or conduct any scientific or trial study of the efficacy of the prehospital emergency use of any drug or treatment procedure within the local EMS system. Such

authority is granted by the California Emergency Services Act, and the California Health and Safety Code section 1797.221, and the California Code of Regulations, Title 22, Division 9, section 100146.

4. COOPERATION AND COMPLIANCE:

A. The EMS Agency and UCLA agree to cooperate with each other for the purpose of conducting the FAST-MAG Trial study in order to meet the requirements outlined under original granting agency in accordance with Grant Number 1 U01 NS 44364.

B. The parties agree to comply with all relevant State and federal statutes and regulations if any, in performing their respective obligations under this MOU.

5. INDEPENDENT CONTRACTOR STATUS: In the performance of this MOU, each party shall be deemed to be an independent contractor and, as such, no employees or staff of one party assigned to perform work under this MOU shall be entitled to any benefits applicable to employees of the other party.

6. INCORPORATION BY REFERENCE: The terms and conditions of the grant program legislation and regulations under which the prime grant award was made, the prime grant Notice of Grant Award ("NGA") including all its special terms and conditions, 45 CFR Part 74, are made a part hereof by reference. A copy of the NGA is attached as Exhibit A.

7. STATEMENT OF WORK:

A. The EMS Agency agrees to use all reasonable efforts to conduct the FAST-MAG Trial as set forth in Exhibit B. The EMS Agency shall ensure that Western Institutional Review Board ("IRB") review and approval for County's operations is current throughout the study and that the County's research activities are conducted in accordance with federal regulations.

B. The EMS Agency shall submit to the UCLA Clinical Coordinating Center within twenty-four (24) hours any reports of which it becomes aware of unanticipated serious adverse events.

C. The EMS Agency shall furnish reports requested by UCLA at such times and in such form as reasonably requested during the term of this MOU (e.g. certification of training in the Protection of Human subjects, IRB updates and renewals, informed consent documents and other regulatory documents).

D. The EMS Agency agrees that in the event that the EMS Agency is terminated in accordance with this MOU, UCLA reserves the right to obtain follow-up data from EMS Agency study participants.

8. PAYMENT AND LIMITATION OF COST:

A. UCLA, through the its Clinical Coordinating Center, shall provide training in FAST-MAG Trial study procedures

and human subject protection to EMS Agency personnel and study participants, including paramedic trainers as set forth in Exhibit B, at no charge to the EMS Agency.

B. The EMS Agency may receive reimbursement from UCLA for its participation in the FAST-MAG Trial study as a subsequent amendment on substantially similar terms of this MOU.

9. TERMINATION:

A. Notwithstanding any other provision of this MOU, either party may terminate this MOU for any reason (with or without cause) by giving the other party at least sixty (60) calendar days prior written notice thereof.

B. In the event of any termination of the FAST-MAG grant award by the National Institute of Health to UCLA, participation by the EMS Agency may be terminated by UCLA at any time by written notice to the EMS Agency.

10. USE OF NAME: California Education Code 92000 prohibits use of UCLA's names to suggest that UCLA endorses a product or service. County shall not use the name The Regents of the University of California, UCLA, UCLA Medical Center, or any similar reference to the University of California or its campuses or physicians, without prior written approval from an authorized representative of UCLA.

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11. PUBLICATION: The EMS Agency shall place an acknowledgment of federal government support on any publication produced under this MOU. In addition, the EMS Agency shall include a disclaimer, as appropriate, as follows: "Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health".

12. COMPLIANCE WITH HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT OF 1966: The parties acknowledge the existence of the Health Insurance Portability and Accountability Act of 1996 and its implementing regulations ("HIPAA"). Contractor understands and agrees that it is or may be considered a "covered entity" as defined by HIPAA and, as such, has obligations with respect to the confidentiality, privacy and security of patients' medical information, and must take certain steps to preserve the confidentiality of this information, both internally and externally, including the training of its staff and the establishment of proper procedures for the release of such information, and the use of appropriate consents and authorizations specified under HIPAA.

The parties acknowledge their separate and independent obligations with respect to HIPAA, and that such obligations relate to transactions and code sets, privacy and security. Contractor understands and agrees that it is separately and independently responsible for compliance with HIPAA in all these

areas and that County has not undertaken any responsibility for compliance on Contractor's behalf. Contractor has not relied, and will not in any way rely, on County for legal advice or other representations with respect to Contractor's obligations under HIPAA, but will independently seek its own counsel and take the necessary measures to comply with the law and its implementing regulations.

Contractor and County understand and agree that each is independently responsible for HIPAA compliance and agree to take all necessary and reasonable actions to comply with the requirements of the HIPAA law and implementing regulations related to transactions and code set, privacy and security. Each party further agrees to indemnify and hold harmless the other party (including their officers, employees and agents), for its failure to comply with HIPAA.

13. INDEMNIFICATION: Notwithstanding any other agreements, County shall defend, hold harmless, and indemnify Contractor, its trustees, officers, employees, physicians, and agents from and against any and all liability, including but not limited to demands, claims, actions, fees, cost, and expenses (including reasonable attorney and expert witness fees), in proportion to and to the extent such demands, claims, actions, fees, costs, or expenses result from the acts and/or omissions of County EMS Agency or their officers, employees or agents arising from and/or relating to the MOU.

Notwithstanding any other agreements, Contractor shall defend, hold harmless, and indemnify County, County's separate legal entities covered by Federalwide Assurance (FWA), County Special Districts, elected or appointed officers, employees, physicians, and agents from and against any and all liability, including but not limited to demands, claims, actions, fees, cost, and expenses (including reasonable attorney and expert witness fees), in proportion to and to the extent such demands, claims, actions, fees, costs, or expenses result from the acts and/or omissions of Contractor, its officers, employees or agents arising from and/or relating to this MOU.

14. PRINCIPAL INVESTIGATOR: Samuel Stratton, M.D. shall be the EMS Agency's Principal Investigator and Human Subjects Administrator, and shall be responsible for the performance of the technical and programmatic aspects of this MOU's Scope of Work. The EMS Agency Director shall be responsible for the overall direction of the EMS Agency's participation in the FAST-MAG Trial study.

15. PROTECTION OF HUMAN SUBJECTS: The EMS Agency shall comply with the applicable terms and conditions of 45 CFR Part 46 "Protection of Human Subjects". The EMS Agency's research subject protocol has been approved by the Western IRB in accordance with federal regulations.

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16. AMENDMENT: This MOU shall not be modified, amended, or waived, whether in whole or in part, except by mutual agreement. Said modifications shall be in the form of a duly executed amendment to this MOU.

17. RECORD RETENTION: County shall retain all pertinent records related to this MOU for three (3) years after the expiration or termination of this MOU and all pending matters are closed, unless extended by an audit, litigation, or other action involving the records, whichever is later.

18. ASSIGNMENT: County shall not assign, transfer or subcontract its rights, interest, or obligations hereunder without the prior written consent of Contractor.

19. WARRANTIES: The EMS Agency warrants that services will be performed in accordance with the scope of work as specified in Exhibit B, and by personnel with the requisite skill, qualifications, certifications and licenses.

20. ADMINISTRATIVE AND TECHNICAL CONTACTS: The following individuals shall serve as contacts for communications regarding this MOU:

TECHNICAL:

UCLA:
Jeffrey L. Saver, M.D.
1072 Gayley Avenue
Los Angeles, CA 90024-1769
PHONE: 310-794-6108
FAX: 310-794-6104
EMAIL jsaver@ucla.edu

EMS AGENCY:
William Koenig, M.D.
5555 Ferguson Drive, Ste 220
Commerce, CA 90022
PHONE: 323-890-7547
FAX: 323-890-8528
EMAIL wkoenig@ladhs.org

ADMINISTRATIVE:

UCLA:

Sharon Lam
Office of Contract and Grant
Administration
10920 Wilshire Blvd., Ste 1200
Los Angeles, CA 90024-1406
PHONE: 310-794-3596
FAX: 310-794-0631
EMAIL slam@resadmin.ucla.edu

EMS AGENCY:

Carol (Gunter) Meyer, Director
5555 Ferguson Drive, Ste. 220
Commerce, CA 90022
PHONE: 323-890-7545
FAX: 323-890-8536
EMAIL cmeyer@ladhs.org

21. NOTICES: Any and all notices required, permitted, or desired to be given hereunder by one party to the other shall be in writing and shall be delivered to the other party personally or by United States mail, certified or registered, postage prepaid, return receipt requested, to the parties at the following addresses and to the attention of the persons named. County's Director shall have the authority to issue all notices which are required or permitted by County hereunder. Addresses and persons to be notified may be changed by a party by giving at least ten (10) calendar days prior written notice thereof to the other.

A. Notices to County shall be addressed as follows:

- (1) Department of Health Services
Contracts and Grants Division
313 North Figueroa Street
Sixth Floor - East
Los Angeles, California 90012
Attention: Division Director
- (2) Department of Health Services
Emergency Medical Services Division
5555 Ferguson Drive, Suite 220
Commerce, California 90022

Attention: Division Chief

(3) Department of Health Services
Financial Services
313 North Figueroa Street - Room 534
Los Angeles, California 90012

Attention: Financial Officer

(4) Auditor-Controller
Kenneth Hahn Hall of Administration
500 West Temple Street
Los Angeles, California 90012

Attention: Auditor-Controller

B. Notices to UCLA shall be addressed as follows:

University of California Los Angeles
Office of Contract and Grant Administration
10920 Wilshire Boulevard, Suite 220
Los Angeles, California 90024-1406

Attention: Sharon Lam

IN WITNESS THEREOF, the Board of Supervisors of the County
of Los Angeles has caused this MOU to be subscribed by its

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Director of Health Services, and Contractor has caused this MOU to be subscribed in its behalf by its duly authorized officer, the day, month, and year first above written.

COUNTY OF LOS ANGELES

By _____
Thomas L. Garthwaite, M.D.
Director and Chief Medical Officer

THE REGENTS OF THE UNIVERSITY
OF CALIFORNIA

Contractor

By _____
Signature

Printed Name

Title _____
(AFFIX CORPORATE SEAL HERE)

APPROVED AS TO FORM:
BY THE OFFICE OF THE COUNTY COUNSEL

APPROVED AS TO CONTRACT
ADMINISTRATION:

Department of Health Services

By _____
Irene E. Riley, Director
Contract Administration

pps:09/22/04
AGRCD3592.PPS

EXHIBIT A

***** NOTICE OF GRANT AWARD *****

RESEARCH PROJECT COOPERATIVE AGREEMENT Issue Date:09/22/2003
Department of Health and Human Services
National Institutes of Health

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

Grant Number: 1 U01 NS044364-01A1
Principal Investigator: SAVER, JEFFREY L MD
Project Title: Field Administration of Stroke Therapy - Magnesium Trial

GRANT ANALYST
UNIV OF CALIFORNIA
OFC OF CONTRACT/ GRANT ADMIN
10920 WILSHIRE BLVD, STE 1200
LOS ANGELES, CA 900241406
UNITED STATES
Award e-mailed to: NIHAward@resadmin.ucla.edu

Budget Period: 09/30/2003 - 06/30/2004
Project Period: 09/30/2003 - 06/30/2007

Dear Business Official:

The National Institutes of Health hereby awards a grant in the amount of \$3,992,591(see ''Award Calculation'' in Section I) to UNIVERSITY OF CALIFORNIA LOS ANGELES in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 31 USC 6305 & 6306 and is subject to terms and conditions referenced below.

Acceptance of this award including the Terms and Conditions is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Award recipients are responsible for reporting inventions derived or reduced to practice in the performance of work under this grant. Rights to inventions vest with the grantee organization provided certain requirements are met and there is acknowledgment of NIH support. In addition, recipients must ensure that patent and license activities are consistent with their responsibility to make unique research resources developed under this award available to the scientific community, in accordance with NIH policy. For additional information, please visit <http://www.iedison.gov>.

If you have any questions about this award, please contact the individual(s) referenced in the information below.

Sincerely yours

MICHAEL LOEWE

Grants Management Officer
NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

See additional information below

SECTION I - AWARD DATA - 1 U01 NS044364-01A1

AWARD CALCULATION (U.S. Dollars):

Salaries and Wages	\$1,578,487
Fringe Benefits	\$333,918
Personnel Costs	\$1,912,405
Consultant Services	\$20,625
Equipment	\$36,000
Supplies	\$179,000
Travel Costs	\$27,930
Patient Care (Inpatient)	\$1,733
Patient Care (Outpatient)	\$278
Other Costs	\$187,871
Consortium/Contractual Cost	\$985,321
Federal Direct Costs	\$3,351,163
Federal F&A Costs	\$641,428
APPROVED BUDGET	\$3,992,591
TOTAL FEDERAL AWARD AMOUNT	\$3,992,591

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project, is as follows.

02	\$3,715,583
03	\$3,719,613
04	\$3,872,344

FISCAL INFORMATION:

CFDA 93.853

Number:

EIN: 1956006143A1

Document Number: UNS044364A

IC/ CAN /	FY2003 /	FY2004 /	FY2005 /	FY2006
NS/8426310/	3,992,591/	3,715,583/	3,719,613/	3,872,344

NIH ADMINISTRATIVE DATA:

PCC: ST17 C / OC: 41.4L / Processed: LOEWEM 030917 1023

SECTION II - PAYMENT/HOTLINE INFORMATION - 1 U01 NS044364-01A1

For Payment and HHS Office of Inspector General Hotline Information, see the NIH Home Page at <http://grants.nih.gov/grants/policy/awardconditions.htm>

SECTION III - TERMS AND CONDITIONS - 1 U01 NS044364-01A1

This award is based on the application submitted to, and as approved by, the NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

- a. The grant program legislation and program regulation cited in this Notice of Grant Award.
- b. The restrictions on the expenditure of federal funds in appropriations acts, to the extent those restrictions are pertinent to the award.
- c. 45 CFR Part 74 or 45 CFR Part 92 as applicable.
- d. The NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
- e. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW. (see NIH Home Page at <http://grants.nih.gov/grants/policy/awardconditions.htm> for certain references cited above.)

This grant is awarded under the terms and conditions of the Federal Demonstration Partnership Phase IV.

Carry over of an unobligated balance into the next budget period requires Grants Management Officer prior approval.

Treatment of Program Income:
Other Research (Add/Deduct Option)

SECTION IV - NINDS SPECIAL TERMS AND CONDITIONS

NOTICE: Because of the number of pages included in the electronic Notice of Grant Award (NGA), additional Cooperative Agreement Terms and Conditions of Award cannot be transmitted electronically. A hard copy is attached to the Notice of Grant Award. These special Terms of Award are in addition to and not in lieu of otherwise applicable OMB administrative guidelines, HHS Grant Administration Regulations at 45 CFR Parts 74, and other HHS, PHS, and NIH Grant Administration policy statements and Terms and Conditions attached or otherwise written on the Notice of Grant Award.

The Phase III Clinical Trial Terms relevant to this project are located in Section I, Section II and Section III at http://www.ninds.nih.gov/funding/clinical_trials/Terms_III.htm These terms are in addition to all other Terms and Conditions preprinted or attached to this Notice of Grant Award for grant #(NS12345). It is the responsibility of the Awardee to comply with all terms and conditions of award as provided.

Noncompliance with these terms of award may result in reduction of the recommended budget, withholding of support, suspension, or termination of award.

Restriction: IRB approval at UCLA Stroke Center - The present award is being made without a currently valid certification of IRB approval for this project with the following restriction: Only activities that are clearly severable and independent from activities that involve human subjects) may be conducted pending acceptance of the certification of IRB approval. The certification of IRB approval must be submitted to the NINDS within 60 days of the issue date of this award.

No funds may be drawn down from the payment system and no obligations may be made against Federal funds for research involving human subjects at any site engaged in such research for any period not covered by an Office for Human Research Protections Assurance and an IRB approval consistent with the requirements of 45 CFR Part 46.

Failure to submit the certification of IRB approval to the within the (insert number here)-day period or to otherwise comply with the above requirements can result in suspension and/or termination of this award, withholding of support, audit disallowances, and/or other appropriate action.

Restriction: This award is issued subject to the following special condition - IRB Approvals for all Participating Sites:

Notice: Under governing regulations, federal funds administered by the Department of Health and Human Services shall not be expended for Research involving human subjects, and individuals shall not be enrolled in such research, (1) without prior approval by the Office for Human Research Protections (OHRP) of an assurance to comply with the requirements of 45 CFR 46 to protect human research subjects, and (2) without the project having been reviewed and approved by the IRB and IRB certification having been submitted to and accepted by the NINDS. This restriction applies to all collaborating sites without OHRP-approved assurances and without IRB certification, whether domestic or foreign, and compliance must be ensured by the awardee.

Only activities which do not directly involve human subjects (i.e., are Clearly severable and independent from those activities that do involve human subjects) may be conducted until the IRB certification has been provided to the NINDS. No funds may be drawn down from the payment system and no obligations may be made against federal funds for any research involving human subjects in this project at all performance sites for which a budget was presented pending NINDS receipt and acceptance of the certification of IRB approval.

Restriction: This award is issued subject to the following special condition Human Subject Assurance for all Participating Sites:

Notice: Under governing regulations, federal funds administered by the Department of Health and Human Services shall not be expended for research involving human subjects, and individuals shall not be enrolled in such research, without prior approval by the Office for Human Research Protections (OHRP) of an assurance to comply with the requirements of 45 CFR 46 to protect human research subjects. This

restriction applies to all collaborating sites without OHRP-approved assurances, whether domestic or foreign, and compliance must be ensured by the awardee.

This award is being made without an OHRP-approved assurance of compliance with 45 CFR 46 for (performance site) with the following restriction: only activities which do not directly involve human subjects (i.e., are clearly severable and independent from those activities that do involve human subjects) may be conducted by performance site pending OHRP's approval of an assurance of compliance with 45 CFR 46.

Funds awarded for \$789,260 direct costs and \$196,061 associated F&A costs for consortium costs are restricted accordingly and may not be used for any other purpose without the written prior approval of the NINDS.

REQUIREMENT/RESTRICTION: This award is made pending the required Certification of Human Subject Training.

NIH requires a letter that includes the names of the key personnel who are responsible for the design and conduct of the study; the title of the education program completed by each named personnel plus a one sentence description of the program. This letter must be signed by the principal investigator and co-signed by an institution official. (Note: In accordance with the September 5, 2001 NIH Guide Notice, only the signature of an institution official is now required.)

The timing of submission of documentation is in keeping with just-in-time procedures and is required prior to award.

This award is funded by the National Institute of Neurological Disorders and Stroke (NINDS). Any papers published under the auspices of this award must cite the funding support of the institute.

The program official is responsible for the scientific, programmatic and technical aspects of this project. The grants management specialist is responsible for the negotiation, award and administration of this project and for interpretation of grants administration policies and provisions. These individuals work together in overall project administration. For additional information, you may access the NIH home page at <http://www.nih.gov/> and the NINDS Home Page at <http://www.ninds.nih.gov>.

For scientific and programmatic issues for the above grant, contact Dr. Robin Conwit, Program Director. E-mail address: rc296d@nih.gov or Phone: 301-496-9135.

For budgetary and policy issues for the above grant contact Ms. Gladys Melendez, Grants Management Officer. E-mail address: gbl3y@nih.gov or Phone: 301-496-3929.

Future year non-competing continuation applications and other documents applicable to this grant should be submitted to:

Grants Management Branch
 National Institutes of Neurological Disorders and Stroke
 6001 Executive Boulevard, Suite 3290, MSC 9537
 Rockville, MD 20852 (Express Mail)
 Bethesda, MD 20892-9537 (Regular Mail)

Robin Conwit, Program Official
 Phone: 301-496-9135 Email: rc296d@nih.gov

Gladys Melendez, Grants Specialist
 Phone: (301)496-3929 Email: gb13y@nih.gov Fax: (301) 402-0219

SPREADSHEET
 GRANT NUMBER: 1 U01 NS044364-01A1

P.I.: SAVER, JEFFREY L
 INSTITUTION: UNIVERSITY OF CALIFORNIA LOS ANGELES

	YEAR 01	YEAR 02	YEAR 03	YEAR 04
	=====	=====	=====	=====
Salaries and Wages	1,578,487	1,698,791	1,743,156	1,788,745
Fringe Benefits	333,918	354,222	363,726	373,498
Personnel Costs	1,912,405	2,053,013	2,106,882	2,162,243
Consultant Services	20,625	21,244	21,882	22,538
Equipment	36,000			
Supplies	179,000	27,800	28,418	29,055
Travel Costs	27,930	28,768	29,631	30,520
Patient Care (Inpatient)	1,733	1,733	1,733	1,928
Patient Care (Outpatient)	278	278	278	308
Other Costs	187,871	182,332	184,557	186,849
Consortium/Contractual Cost	985,321	796,186	729,676	806,790
TOTAL FEDERAL DC	3,351,163	3,111,354	3,103,057	3,240,231
TOTAL FEDERAL F& TOTAL COST	641,428 3,992,591	604,229 3,715,583	616,556 3,719,613	632,113 3,872,344

	YEAR 01	YEAR 02	YEAR 03	YEAR 04
	=====	=====	=====	=====
F&A Cost Rate 1				
F&A Cost Base 1	26.00%	26.00%	26.00%	26.00%
F&A Costs 1	2,467,029	2,323,959	2,371,370	2,431,205
	641,428	604,229	616,556	632,113

**STATEMENT OF WORK/
ROLES AND RESPONSIBILITIES OF THE PARTIES**

The parties acknowledge that Contractor is the prime recipient of the grant from the Department of Health & Human Services for funding of the FAST-MAG Trial and, as such, is generally responsible for performing all activities in accordance with the FAST-MAG Trial Protocol, attached hereto as Attachment B. However, the parties have specifically set forth the following certain responsibilities of the Contractor and the County:

Section:

2.1 Inclusion Criteria

Contractor shall develop and supply the Los Angeles Prehospital Stroke Screen (LAPSS) for use by paramedics as approved by the County. Contractor shall obtain all necessary regulatory and other approvals prior to use. It is anticipated that a completed LAPSS for each patient participating in the Trial shall be provided to at least the County EMS Agency and the Contractor (*e.g.* collected by the Study Nurse at the participating hospital).

3. Enrollment and Consent

Contractor shall supply and maintain in-vehicle FAST-MAG cellular phone upon request of paramedic.

Contractor shall determine participant eligibility by applying inclusion and exclusion criteria.

Contractor shall develop and supply informed consent forms for signature by all study participants or their authorized representative. The forms shall be translated into at least English and Spanish. Contractor shall obtain all necessary regulatory and other approvals (*e.g.* participating hospital IRB approval).

Contractor shall be responsible for eliciting consent from study participant as confirmed by participant's/authorized representative's signature of the consent form.

Contractor shall authorize administration of magnesium sulfate.

5. Study Treatment

Contractor shall supply and maintain drug kits for administration of the magnesium sulfate.

6. Treatment Evaluation

Paramedics shall record heart rate, blood pressure, Los Angeles Motor Scale and Glasgow Coma Scale on the EMS Report Form. Contractor shall obtain a copy of the completed EMS Report Form from the treating paramedic at the receiving hospital.

9.5 Training Paramedics in Study-Related Procedures and Maintaining Study-Related Knowledge Base

Contractor shall continuously train paramedics and County staff on all relevant aspects of the trial, including use of the LAPSS, coordination with Contractor in determining participant eligibility, obtaining participant consent and signature by participant of the consent form, collaboration with Contractor's representatives (*e.g.* physician investigator, nurse coordinators, paramedic clinical supervisors, reporting of serious adverse events).

County shall monitor paramedics for proper LAPSS and Los Angeles Motor Scale certification.

Except as agreed to by the parties, Contractor shall be responsible for all aspects of the trial once the participant arrives at the hospital. County shall not be responsible for subsequent participant evaluations (*e.g.* follow-up interviews), adjudication of potential serious adverse events by the blinded adjudication committee and review by the data and safety monitoring board, receipt and transcription of prehospital data to case report form, and data collection, and all other activities relating to data collected, for the period during participant's treatment at the hospital and posthospital.

County shall collect and submit data, blood test results and other data as agreed to by the parties.

FAST-MAG Trial Protocol

1. Trial Overview

This is a multicenter, randomized, placebo-controlled, double-blind, parallel group trial of intravenous magnesium sulfate initiated by paramedics in the field within 2 hours of symptom onset in 1298 patients with acute stroke. The primary objective of the study is to evaluate the efficacy and safety of field-initiated magnesium sulfate in improving the long-term functional outcome of patients with acute stroke. The study will be conducted employing the paramedic systems of the County of Los Angeles. These systems provide prehospital care to a population of 9.8 million. Patients with acute stroke will be identified in the field by licensed paramedics who have received training in basic and advanced cardiac life support, stroke recognition, and specific procedures relevant to the proposed study. Physician-investigators will approve each patient for study entry after cellular phone contact with paramedics. Physician-investigators will also by phone elicit consent to participate in the study, from patients when the subject is competent and from on scene or off scene legally authorized persons when the subject is not competent. Paramedics will initiate a loading dose of 4 grams magnesium sulfate iv over 16 minutes or matched placebo, followed after hospital arrival by a maintenance infusion of 16 grams magnesium sulfate iv over 24 hours or matched placebo. Follow-up assessments will be performed at ED arrival, 24 hours, 48 hours, day 4, day 30, and day 90. The enrollment period will last 3.5 years and the follow-up period an additional 3 months. The sites involved in the study will be all (~330) rescue engines of the Los Angeles County EMS system and all (~82) hospitals with a licensed adult patient Emergency Department in the County of Los Angeles. The Clinical Coordinating Center and the Neuroimaging Analysis Center will be at UCLA Medical Center and the Data Management Center will be coordinated through Stanford University.

1.1 Study Hypotheses

The central aim of this study is to demonstrate that paramedic initiation of the neuroprotective agent magnesium sulfate in the field is an efficacious and safe treatment for acute stroke. The study design is a multicenter, randomized, double-blind, phase 3 clinical trial, using intention to treat analysis, of magnesium sulfate versus placebo among ambulance-transported patients with acute stroke, with study agent initiated in all individuals within two hours of stroke onset. Successful conduct of the trial will serve as a pivotal test of the promising neuroprotective agent magnesium sulfate in acute stroke, and will also demonstrate for the first time that field enrollment and treatment of acute stroke patients is a practical and feasible strategy for phase 3 stroke trials, permitting enrollment of greater numbers of patients in hyperacute time windows.

1.1.1 Primary Hypothesis:

Treatment with magnesium sulfate improves the long-term functional outcome of hyperacute stroke patients.

The primary study endpoint analyzed to test this hypothesis will be the difference in distribution of scores between magnesium sulfate and placebo groups on the modified Rankin Scale measure of global handicap, assessed 3 months poststroke.

1.1.2 Secondary Hypothesis:

Treatment with magnesium sulfate improves the long-term outcome of hyperacute stroke patients on measures of activities of daily living, neurologic deficit, quality of life, and mortality.

The secondary study endpoints analyzed to test these hypotheses will be the difference in distribution of scores between magnesium sulfate and placebo groups on the Barthel Activities of Daily Living Scale, the National Institute of Health Stroke Scale (neurologic deficit), the Stroke Impact Scale (stroke-specific quality of life), and in mortality, assessed 3 months poststroke.

Treatment with magnesium sulfate improves the long-term functional outcome of each of the following subgroups of hyperacute stroke patients:

1. Patients with ischemic stroke
2. Patients with intracerebral hemorrhage
3. Patients with ischemic stroke treated with conventional intravenous tissue plasminogen activator
4. Patients with ischemic stroke not treated with conventional intravenous tissue plasminogen activator
5. Patients with ischemic stroke treated within 60 minutes of onset
6. Patients with ischemic stroke treated within 61-120 minutes of onset

To test these hypotheses, the primary study endpoint, differences in the distribution of scores between magnesium sulfate and placebo groups on the modified Rankin Scale measure of global handicap, will be separately analyzed in each of these subgroups.

2. Entry Criteria

2.1 Inclusion Criteria

All patients transported by EMS in Los Angeles County will be screened for study entry. Study inclusion criteria are:

- 1) Suspected stroke identified by the Los Angeles Prehospital Stroke Screen
- 2) Age 40-95, inclusive
- 3) Last known well time within 2 hours of treatment initiation
- 4) Deficit present for ≥ 15 minutes

2.2 Exclusion Criteria

Study exclusion criteria are:

- 1) Coma
- 2) Rapidly improving neurologic deficit
- 3) SBP < 90 or > 220
- 4) Known severe renal dysfunction (on dialysis or known chronic creatinine > 3.0)
- 5) Severe respiratory distress (O₂ sat $< 90\%$ or respiratory rate ≥ 20)
- 6) Known second or third degree heart block with no pacemaker in place
- 7) Major head trauma in the last 24 hours
- 8) Recent stroke within prior 30 days
- 9) Patient unable to give informed consent and no available legally authorized representative to provide informed consent

The rationale for these exclusion criteria are as follows. Stroke patients comatose at presentation have a dismal prognosis, unlikely to be benefitted by study agent. Patients with rapidly improving neurologic deficits likely will have an excellent recovery with conventional care, precluding the ability to detect a beneficial treatment effect of magnesium. Patients with severe hypotension have at least a theoretical risk of being adversely affected by hypotensive effects of magnesium sulfate, even though these are uncommon, and minimal if present at all, at the study dose. In patients with severe hypertension a portion of the presenting neurologic deficit may be due to hypertensive encephalopathy rather than focal stroke, confounding interpretation of baseline neurologic status and response to study agent. Patients with known advanced renal dysfunction are excluded because magnesium sulfate is cleared renally. The total 24 hour study dose could theoretically produce potentially toxic magnesium serum levels in these patients. The loading dose alone is anticipated to be safe even in anuric patients. Consequently the rare patient with new onset, unidentified renal failure that is not discovered until hospital arrival will not be adversely affected by trial enrollment, as trial procedures dictate the immediate cessation of the maintenance dose when creatinine is discovered to exceed 3.0. Patients with severe respiratory distress are excluded lest subclinical effects of magnesium sulfate on neuromuscular transmission and muscle strength reduce respiratory effort. Including this exclusion criteria is an extremely conservative measure, as magnesium sulfate at trial doses exerts no clinical effect or documented subclinical effect on muscle strength. Patients with known unprotected second or third degree heart block are excluded because, at high serum levels, magnesium inhibits the cardiac conduction system and could worsen heart block. Patients with recent strokes in the past 30 days are excluded because they may have not yet recovered to a stable baseline from their prior stroke, and evolution of the old deficit will confound interpretation of study agent effect on evolution of the new deficit. It is anticipated that collectively these exclusion criteria will exclude only a small fraction of patients from trial eligibility.

Pregnant patients and potentially pregnant patients may be enrolled in the trial. Injectable magnesium sulfate is classified by FDA labeling as pregnancy category C - risk cannot be ruled out. This appellation is given when, "Adequate well-controlled human studies are lacking, and animal studies have shown a risk to the fetus or are lacking as well. There is a chance of fetal harm if the drug is administered during pregnancy; but the potential benefits may outweigh the risks." As standard care for preeclampsia and eclampsia, magnesium sulfate is frequently used in the third trimester and occasionally in the second trimester, with no net evidence of fetal risk reported in the literature.

3. Enrollment and Consent

After initial patient contact and assessment, paramedics will contact the on-call FAST-MAG physician-investigator using an in-vehicle FAST-MAG cellular phone. By phone, the physician-investigator will review the patient's relevant medical history and current clinical condition with the paramedics and the patient. The physician-investigator will verify the diagnosis of acute stroke and determine eligibility for study entry according to inclusion and exclusion criteria above.

All study participants will be enrolled employing explicit consent procedures. The consent provider will be the patient if he or she is competent and the patient's legally authorized representative if the patient is not competent. When a legally authorized representative is on scene, he or she will be immediately approached for consent. If no legally authorized

representative is on scene, attempts will be made to reach a legally authorized representative at a different location by phone and fax. Each rescue vehicle will carry study informed consent forms, and these will be handed to the consent provider. The physician-investigator will discuss the study by phone with the consent provider. Once informed consent is obtained, the physician-investigator will authorize study drug administration. IRB approval for the study will be obtained from all participating receiving hospitals, and the consent form approved by the salient receiving hospital IRB will be employed in study enrollment.

4. Randomization

Randomization is designed to maintain blinding of the patient, the PI, the local PI, paramedics, local study staff, local allied health personnel, the Clinical Coordinating Center, and the Data Management Center (DMC). Dr. Hamilton, the chief study statistician at the DMC, will generate the randomization algorithm for the study and will be unblinded. Study drug will be prepared according to a prearranged randomization assignment developed by Dr. Hamilton. Randomization will be in permuted block design allocating magnesium sulfate or placebo in a 1:1 ratio, and will be stratified within each rescue vehicle by elapsed time from stroke symptom onset (15-60 minutes, 61-120 minutes).

A general study goal is to enroll a substantial number of patients in each of the ≤ 1 hour from onset and 1-2 hr from onset strata. The proportion of patients enrolled in each strata will be continuously monitored by the DMC. If the proportion of patients enrolled in one strata exceeds 70%, enrollment in that strata may be placed on hold studywide until enrollment in the other strata exceeds 31%.

5. Study Treatment

Magnesium sulfate (Mg) or matching placebo will be administered intravenously with a 16 minute bolus load followed by a 24 hour infusion. The bolus-loading dose will contain 4 grams Mg in 8 ml normal saline. The maintenance infusion will contain 16 grams Mg diluted in 282ml 0.9% normal saline, infused at 12 ml/hr for 24 hours. Paramedics in the field will initiate the bolus-loading dose, administered by slow intravenous push over 16 minutes. The maintenance infusion will be initiated in hospital immediately upon completion of the loading dose.

Drug kits will be specially prepared for the study and carried in each participating vehicle. Each kit will include two syringes preloaded with study agent or placebo, one vial containing study agent or placebo, one bag of 250 ml normal saline, a study information sheet, and two preprinted adhesive labels. The two pre-loaded syringes are for the field dose, and will each contain 2 grams Mg in 4 ml normal saline, or matching placebo. These will be administered directly by the paramedics by slow iv push over 16 minutes, including 8 per syringe. The vial is for the in-hospital maintenance dose, and will contain 16 grams of Mg in 32 ml 0.9% normal saline. Emergency Department nursing personnel will add the contents of the vial to the 250 ml saline bag and infuse the trial solution by intravenous cannula over 24 hours using a controlled rate infusion pump.

Each of the ~366 ambulances participating in the study will be stocked with two drug kits at all times, one for under one hour patients and the second for 1-2 hour patients. These kits will be color-coded, with green for under 1 hour patients and yellow for 1-2 hour patients. After each patient enrollment, the vehicle will be restocked on the same or following day. Kits will be stored at 15-30 degrees Centigrade in the pharmacy/central warehouse of the Los Angeles City

Fire Department. When stocked in rescue vehicles, kits will be stored at ambient temperature (generally 15-30 degrees Centigrade) for 12 months. Stability analyses show that magnesium sulfate suffers no significant loss of potency when stored at room temperature for a minimum of 60 months. Kits that expire unused in ambulances after 12 months will be replaced.

As soon as a patient is enrolled, the enrolling physician will activate the study nurse at the hospital to which the patient is being transported. The study nurse will travel to the receiving hospital to assist Emergency Department and Hospital nurses in implementing study procedures and to record CRF data. During field treatment and transport, base station medical personnel will receive patient status updates by radio contact.

5.1 Rules for Stopping Treatment

Study agent infusion will be stopped earlier than the planned 24 hour course under the following circumstances: a drop in systolic BP of greater than 10 mm Hg or diastolic BP of greater than 5 mm Hg occurs associated with worsening of neurologic exam, not responsive to intravenous fluids or albumin; systolic blood pressure drops below 90 or diastolic below 55 without response to intravenous fluids or albumin; cardiac arrhythmia appears that may be related to or exacerbated by magnesium; urine output < 10 cc/hr unresponsive to intravenous fluids or diuretics; significant change in mental status (confusion, stupor, coma) accompanied by loss or diminution of reflexes thought to be due to magnesium toxicity; the patient's attending physician believes for any reason that study agent infusion is producing an adverse effect that may negatively affect patient outcome.

5.2 Concomitant Therapy

Patients enrolled in this trial may receive any conventional stroke treatment at the discretion of their attending physicians. Patients may not be enrolled in another therapeutic clinical trial until after exit from FAST-MAG after the 90 day visit. Patients may not be treated with other experimental stroke therapies.

Treatment with tissue plasminogen activator within 3 hours of symptom onset, after exclusion of intracranial hemorrhage, is encouraged in patients who meet thrombolytic treatment criteria outlined in national consensus guidelines. Since in vitro compatibility has not been tested, a separate IV line should be employed if tissue plasminogen activator and the FAST-MAG trial solution are being infused simultaneously. Prespecified secondary analyses will examine the effect of study treatment in ischemic stroke patients treated with and treated without thrombolytic therapy.

Evidence for the safety of concomitant magnesium sulfate and fibrinolytic therapy comes from the absence of adverse interaction among more than 41,000 MI patients receiving both magnesium sulfate and fibrinolytic agents in large cardiac trials, as reviewed above. [1,2] Additionally, the US manufacturer of TPA has on file no reports of adverse interactions between magnesium sulfate and tissue plasminogen activator in preclinical or clinical datasets (personal communication, Charles Semba, M.D, Genentech, 9/02) and the FDA Medwatch program has not logged any reports of adverse magnesium-TPA interactions (FDA FOIA inquiry, 9/02).

6. Treatment Evaluation

6.1 Field Baseline Evaluation

At study entry, immediately prior to initiation of study agent, paramedics will record:

- Heart rate
- Blood pressure
- Los Angeles Motor Scale (LAMS)
- Glasgow Coma Scale (GCS)

6.2 Hospital Arrival Evaluation

At hospital arrival the following data will be recorded

- Heart rate
- Blood pressure
- Paramedic Global Impression of Change (PGIC) Scale — a 5 point Likert scale measuring paramedic perception of general evolution of neurologic deficit from time of therapy start in the field to time of ED arrival (much improved, mildly improved, unchanged, mildly worsened, much worsened)
- Arrival NIH Stroke Scale (NIHSS) [3]
- Arrival Los Angeles Motor Scale (LAMS)
- Arrival Glasgow Coma Scale (GCS)
- CT/MR result checklist
- Demographic data (age, sex, vascular risk factors)
- Premorbid status (premorbid Rankin Scale) [4]
- Stroke subtype classification (Oxfordshire Stroke Project Classification form) [5]

We expect that all patients will have a brain CT or MRI performed as soon as possible after admission, as recommended by US consensus guidelines for imaging of stroke patients from the American Heart Association and the National Stroke Associations, and international guidelines from the World Health Organization (Helsingborg declaration). [6,7] Scans will be copied for blinded independent radiologic review and coding.

6.3 24 Hour Evaluation

- Heart rate
- Blood pressure
- NIH Stroke Scale (NIHSS)

6.4 48 Hour Evaluation

- Heart rate
- Blood pressure
- NIH Stroke Scale (NIHSS)
- Modified Rankin Scale (mRS)
- Barthel Index [10]
- Glasgow Outcome Scale ([11]

6.5 Day 4 Evaluation

- Heart rate
- Blood pressure
- NIH Stroke Scale (NIHSS)
- Los Angeles Motor Scale (LAMS)
- Modified Rankin Scale (mRS)
- Barthel Index (BI)
- Glasgow Outcome Scale (GOS)

6.6 Day of Discharge Information

- Day of Discharge
- Discharge destination (home, acute rehab, subacute rehab, SNF)
- Concomitant therapies form

6.7 Day 30 Evaluation (Phone)

- Interval Events Form
- Concomitant therapies form
- Modified Rankin Scale (mRS)
- Barthel Index (BI)
- Glasgow Outcome Scale (GOS)

6.8 Day 90 Evaluation

- Interval Events Form
- Concomitant therapies form
- NIH Stroke Scale (NIHSS)
- Los Angeles Motor Scale (LAMS)
- Modified Rankin Scale (mRS)
- Barthel Index (BI)
- Glasgow Outcome Scale (GOS)
- Stroke Impact Scale (SIS) – Stroke Specific Quality of Life Measure [12]

Outcome evaluations will be performed by study physicians and study nurses certified in the reliable and accurate performance of salient rating scales. All outcome raters will undergo training and certification in the NIHSS, the LAMS, the mRS, the BI, and the SIS. Training will utilize already existing, validated videotape training and certification programs for the NIHSS, LAMS, and SIS, and existing, validated paper training and certification programs for the BI and the mRS.

6.9 Central Readings of CT/MRs

Central Coordinating Center readings of all entry CTs/MRs (first brain imaging obtained at hospital arrival) and all CT/MRs subsequently obtained because of patient worsening will be performed by the study neuroradiologist. All sites will be requested to perform CT scans with 5 mm slice thickness. Clinical study sites will send a hard copy of entry CT/MR scans to the coordinating center for analysis within 48 hours of patient enrollment.

6.10 Blood Pressure Evaluations

In addition to the above, blood pressure and heart rate will be recorded every 4 hours for the first 24 hours, and every 8 hours for the second 24 hours, after study initiation. It will be recommended that blood pressure measurements be taken in the non-paretic arm whenever possible.

6.11 Serious Adverse Events

Serious adverse events will be identified at every scheduled follow-up point by study site investigators and study nurses. A serious adverse event is one that is fatal or life-threatening, is permanently or substantially disabling, requires or prolongs hospitalization, or is a congenital anomaly, cancer or medication overdose, or any event that the treating clinician judges to be a significant hazard, contraindication, side effect, or precaution.

As local site principal investigators, each site PI is responsible for reporting all clinical adverse events promptly to the local Institutional Review Board and to the Clinical Coordinating Center. As the overall study principal clinical investigator and holder of the IND, Dr. Saver will review all clinical adverse events and will be responsible for relaying information regarding serious adverse events to the FDA and to all clinical sites. Steven Levine, MD, Professor of Neurology at Mount Sinai Medical School, New York, will act as the independent safety monitor for the trial. Both Dr. Saver and Dr. Levine will review all serious medical events.

All serious adverse events, whether or not considered to be related to study medication, will be reported to the local Institutional Review Board and to the Food and Drug Administration within 3 working days. All fatal adverse events will be reported to the local IRB and the FDA within 24 hours, or, at the latest, on the following working day. At the time of the initial report, the following information will be provided: study ambulance, study hospital, patient number, description of the event, date of onset, current patient status, start date of treatment, whether treatment was discontinued, and if the study blind was broken for the patient, the reason why the event is classified as serious, and the attending physician's current assessment of the association between the event and study treatment. After this first report, significant new information regarding evolution of a serious adverse event will be reported promptly to the local IRB and to the FDA. A quarterly report on studywide SAEs will be generated by the Data Management Center and reviewed by the Dr. David Sherman, Chair of the NIH-appointed Data Safety and Monitoring Board, and by Dr. Levine, the independent safety monitor.

Any patient who experiences an adverse event may be withdrawn at any time from the study at the discretion of the investigator. If the investigator considers that knowledge of the treatment given in the study is necessary for management of the adverse event, the treatment code may be broken for that patient only.

6.12 Endpoint Definitions and Blinded Adjudication Committee

Key adverse events to be tracked in the study are recurrent ischemic stroke and symptomatic hemorrhagic transformation of infarct. A Blinded Adjudication Committee will adjudicate all potential occurrences of these adverse events.

Recurrent ischemic stroke will be defined as a clinical, sudden, and persisting (>24h) deterioration occurring without ICH or other nonischemic cause for symptoms, and 1) attributable to a newly involved territory at any time during the study, or 2) attributable to the entry infarct territory but occurring after study day 5. [13,14]

Symptomatic hemorrhagic transformation of cerebral infarct will be defined as CNS hemorrhage in a patient with an entry CT scan negative for hemorrhage, and either 1) appearing in the area of the qualifying stroke and causally related to neurological deterioration (≥ 4 points worsening on the NIHSS compared with the previous examination or by global clinical assessment), or 2) appearing in a different vascular territory than the qualifying stroke and associated with new neurological deficit. [13,15]

If a clinical deterioration occurs, the local site investigator will complete the appropriate data forms, provide a narrative description of the event, and forward all these materials to the Data Management Center within 10 days of the event. These materials will be reviewed for completion by staff of the Clinical Coordinating Center and then sent to the three members of the Blinded Adjudication Committee who will review these data independently and blinded to treatment assignment. If the Committee members have different opinions, they will be required to reach a consensus as to whether an endpoint or complication occurred.

In the course of trial implementation, additional classes of events may be observed that it would be helpful to formally adjudicate, in the view of the Trial Executive Committee, the DSMB or both. The Blinded Adjudication Committee will then additionally perform these tasks.

6.13 Safety Monitoring

6.13.1 Data and Safety Monitoring Board

To ensure that appropriate ethical consideration is given to the welfare of the patients enrolled in the study, NINDS-NIH has appointed a Data and Safety Monitoring Board (DSMB) to oversee the trial. The DSMB will review the incidences and circumstances of adverse events that occur during the course of the trial. Formal interim analyses will occur after 25%, 50%, and 75% of patients have been enrolled. The members of the DSMB are:

David Sherman, MD (Chair) - Professor and Chair of Neurology, University of Texas, San Antonio, Stroke Neurologist

Karen Johnston, MD - Associate Professor of Neurology and Health Evaluation Sciences, University of Virginia, Stroke Neurologist and Health Outcomes Specialist

Rafael Llinas, MD - Assistant Professor of Neurology, Johns Hopkins, Stroke Neurologist

Oscar Benavente, MD - Associate Professor of Neurology, University of Texas, San Antonio, Stroke Neurologist

Jeffrey Dawson, PhD - Professor of Biomathematics, University of Iowa, Statistician

6.13.2 Independent Safety Monitor

Steven Levine, MD, Professor of Neurology at Mount Sinai Medical Center, New York, will serve as the independent safety monitor for the trial. Dr. Levine is an international expert in acute stroke care and clinical trials. Dr. Levine will review all serious events individually on a continuous basis as they occur and aggregate unblinded data on adverse events quarterly. Dr. Levine will report independently to the DSMB at regularly scheduled DSMB meetings. Dr. Levine also has the authority to alert the DSMB at any time if a potential safety issue arises.

6.14 Collection of Study Data

Prehospital trial data (LAMS score, GCS score, paramedic global impression of change score, field vital signs) will be recorded by paramedics and transcribed to the Case Report Form by site nurse coordinators.

ED arrival, 24 hour, 48 hour, and day 4 data, including NIHSS, MRS, GOS, and BI, will be collected by either the site physician investigator or the site nurse coordinator, at the discretion of the local site principal investigator. NIHSS scores can only be recorded by physician investigators or nurse coordinators certified in NIHSS performance. If a serum magnesium level is obtained in a study patient within the first 72 hours of study initiation, all subsequent in hospital outcome evaluations (24 hour, 48 hour, day 4) will be performed by a non-site nurse coordinator who has had no contact with the patient, the patient chart, or the treating team previously.

All day 30 phone interview outcome ratings and final day 90 study clinic visit outcome ratings will be performed by a non-site nurse coordinator who has had no contact with the patient, the patient chart, or the treating team previously. This precaution is undertaken to ensure that 30 and 90 day outcomes, including the primary trial endpoint 90 day modified Rankin Scale score, are scored by raters fully blinded to patient treatment assignment.

Figure 6 is a schematic outlining study personnel responsibility for collecting post-hospital arrival trial data.

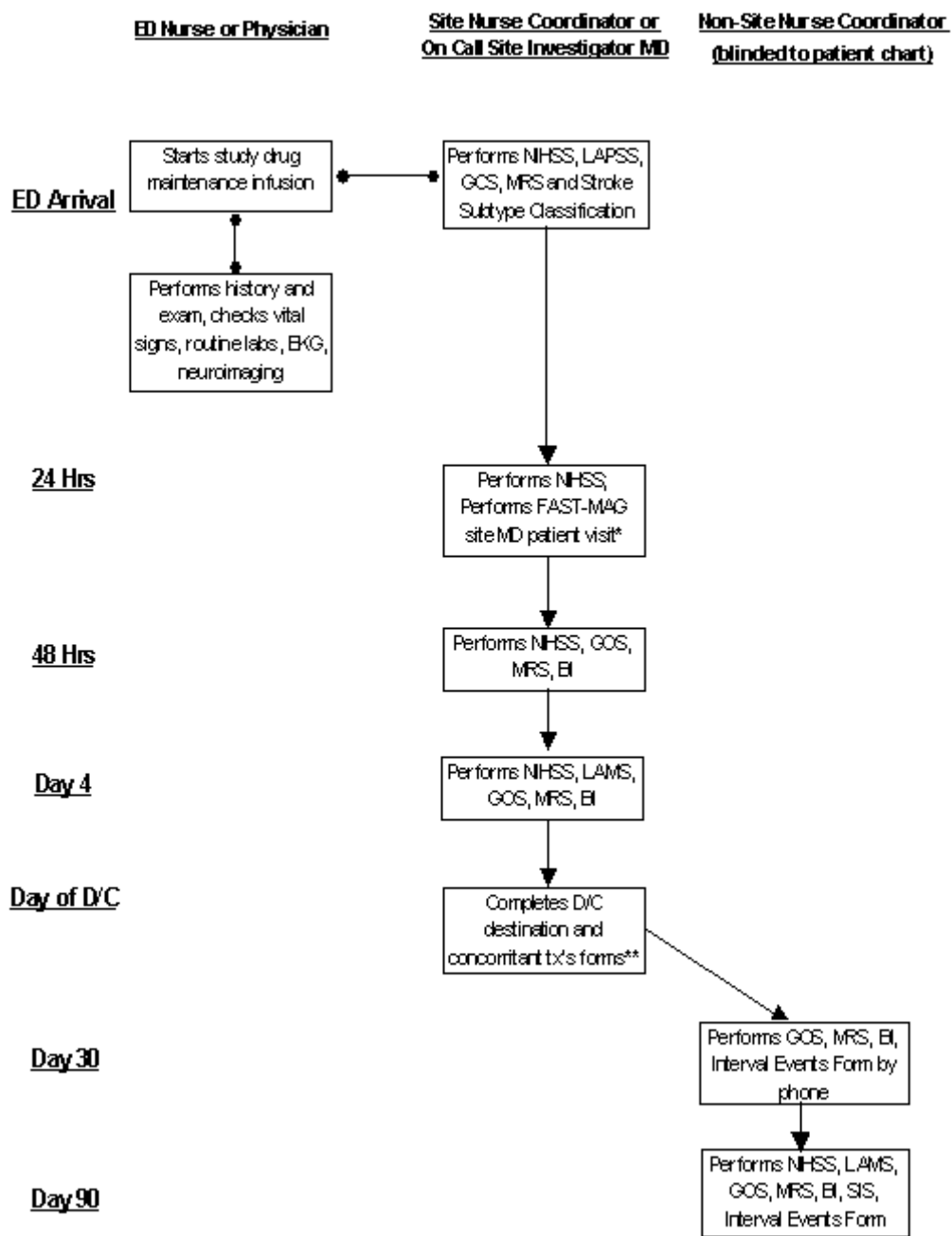


Figure 6: FAST-MAG Post-Arrival Evaluations Flow Diagram

7. Data Collection and Integrity

7.1 Evaluation of the Study Network

Eighteen full time nurse coordinators are dedicated to implementation of FAST-MAG as their full-time responsibility. Each nurse coordinator will cover 3-5 hospitals, and respond emergently to enrolled patients arriving at any of their facilities. The nurse coordinator will also continually update paramedics, ED staff, and neurologists in their catchment area regarding study rationale, study procedures, and study progress. The study coordinators will review all radio calls to their base station hospitals. Any calls in which the diagnosis of stroke was made will be reviewed to determine whether the patient was offered enrollment in the study. Patients appropriate for the study who are not enrolled will be reviewed by Dr. Starkman (chief Emergency Physician Investigator) and the physician-director of the salient EMS service. Feedback will be given to personnel involved in these calls to determine reasons for non-enrollment and correct any problems regarding the protocol.

To ensure an ongoing working knowledge of the protocol, the study nurse-coordinators will meet with the PI and the chief nurse-coordinator on a quarterly basis after initial orientation, to give follow-up regarding compliance with the protocol and review any complications or management problems associated with patients enrolled in the study.

Paramedic performance will be monitored by two methods. In-field supervision will be provided 24 hours a day by highly trained Paramedic Clinical Supervisors who respond, in an emergency vehicle, to all critical calls in the catchment area. They will observe the performance of paramedics, identify and correct deficiencies or problems in care, and serve as a resource for complex or difficult cases. In addition, for each enrolled patient, paramedic performance will be assessed by the physician-investigator working with the paramedic by phone in the field, by direct interaction and by next-day review of the prehospital care record, for compliance with study guidelines.

7.2 Data Collection

All data will be collected on a standardized case report form designed for this study. Clinical data will be obtained on the case report forms, including patient demographics, previous medical conditions, previous stroke or transient ischemic attacks, vital signs, laboratory assessments, NIH Stroke, Barthel, Glasgow Outcome, Stroke Impact and modified Rankin Scales. In addition, an assessment of ischemic stroke subtype will be performed at baseline, employing the Oxfordshire Stroke Classification System.

Additional clinical information including concomitant medications, complications of therapy, neurologic worsening, and a narrative clinical summary of serious adverse events will be included. In addition, detailed data assessment of the baseline CT (or MRI) scans will be performed at the central trial imaging analysis center at UCLA. Filmed copies of all initial CT (or MRI) scans will be forwarded to UCLA for analysis.

7.3 Data Management and Quality Assurance

Study nurses will fill out a stroke log for all study sites that documents all patients transported by a study ambulance to that site and their discharge diagnosis from the ED. For transported stroke patients who are not enrolled in the trial, the reason for exclusion will be recorded. After the first patient has completed the study at each site, a site visit will be performed by the Study Nurse Monitor. She will review the case report form and compare the data entered to the patient's medical record. Any inadequacies or errors will be reviewed with

the co-investigator at the site. Subsequently, on site case report form monitoring visits will be performed after every 4 patients enrolled at that site. The field-enrolling physician will inform the coordinating center of every patient enrollment on the same or next business day, by faxing an enrollment notification form to the coordinating center. The baseline CT (or MRI) will be copied and transported by the study nurse to the coordinating center within 7 days of enrollment.

Computerized data entry from the clinical report forms (CRFs) will be performed by trained data entry personnel at the Data Management Center (Pacific Data Designs). Incoming CRFs will be logged by the Data Management Center. This tracking process maintains a running inventory on pages received so that missing pages may be retrieved to facilitate accurate processing of study data. Data entry will be performed using independent, dual data entry. Data are entered twice with each entry performed by a different person. A third person subsequently compares the two entries, resolves discrepancies, and updates the database as required. Data Management Center data entry operators are trained to enter exactly what is recorded on the CRF. Consequently, all data quality checks are performed after the independent, dual data entry comparisons have been completed. Computerized data quality checks flag discrepant entries for resolution. Every non-text field that is entered into the database has either a range check or internal consistency check, or both, applied to it. Any discrepancies are manually reviewed. Discrepancies will be queried and sent to the head study coordinator at the Clinical Coordinating Center for resolution. Entered data are automatically forwarded to the Data Management Center's Clinical Data System for storage and processing. Clinical Data System is a completely validated Clinical Data Management System that runs under Windows NT. SeaGate Backup software will be employed for daily, weekly, and monthly backups.

Quality assurance of the database additionally includes manual quality assurance conducted on a sample number of randomly selected cases. The sampling algorithm used is based on the number of fields in the database and not the number of patients. The number of patients required to obtain the specified fields are selected and a printout of all entered data is generated. The printout is then compared against the CRF pages to identify and discrepancies. The sampling algorithm assures a minimum manual quality assurance review that encompasses a 100% audit of 10% of data.

All study-related data and documentation will be retained by the Data Management Center for a minimum of two years after FDA approval. Data will be stored on CD-ROM and will be retained in a fire safe environment.

7.4 Handling of Regulatory Documents, Site Records, IRB Documentation

7.4.1 Regulatory Document Binder Maintenance and Access

Each site will be provided with a pre-formatted binder for all regulatory documents pertaining to the FAST-MAG clinical trial. As this binder will contain confidential information, only site Principal and co-investigators, site nurse coordinators, FAST-MAG Clinical Coordinating Center investigators and staff, and members of the FDA will be authorized to have access. This trial is being conducted under an FDA IND and trial results may be submitted to the FDA in support of a New Drug Application. Accordingly, study regulatory documents as well as study data CRFs must be maintained scrupulously and be fully adequate to pass FDA audit. It is the responsibility of the site Principal Investigator, assisted by the site nurse coordinator, to maintain the regulatory document binder in a complete and timely manner.

7.4.2 Regulatory Documents to Be Maintained at All Hospital Sites

Instructions for completing all regulatory documents are included in the FAST-MAG Operations Manual. Completed documents to be filed in the designated sections of the Regulatory Documents Binder include:

- 1) **Study Site Signature Log:** This log is completed with the printed name, role, effective date, initials, and original signature of all personnel to be involved in the conduct of this study.
- 2) **Patient Screening Log:** The study nurse assigned to each site will complete this log with the patient initials, medical record number or social security number, date or screening, and enrolled patient study number, or reason for exclusion, for all patients screened for this study.
- 3) **Protocol / Amendment Signature Page(s):** A photocopied version of the signed protocol page(s) will be filed in this section. Any revisions to the protocol will require a signed protocol amendment page. The original will be forwarded to the FAST-MAG UCLA Central Coordinating Center.
- 4) **Protocol and Amendments:** The original protocol and any subsequent amendments will be filed in this section.
- 5) **Investigator's Brochure / FDA Package Insert for Magnesium Sulfate:** This document and any subsequent revisions will be filed in this section.
- 6) **FDA Form 1572:** An FDA Form 1572 will be completed for each FAST-MAG receiving hospital site and signed by the site's principal investigator. The original form and any subsequent revisions will be forwarded to the FAST-MAG UCLA Central Coordinating Center, and a copy will be filed in this section.
- 7) **Curriculum Vitae:** Copies of the curriculum vitae of the site's principal and all sub-investigators listed on Form FDA 1572 will be filed here.
- 8) **Institutional Review Board / Ethics Committee Approval Letters:** Documentation of the IRB approval of the protocol, protocol amendments, and informed consent will be filed in this section. Copies of all IRB documentation will be forwarded to the FAST-MAG UCLA Central Coordinating Center.
- 9) **IRB Correspondence:** Documentation of request for IRB review of the protocol, protocol amendments, and Informed Consent will be filed in this section. Correspondence and Reports to the IRB, and any protocol-specific correspondence between the Principal Investigator and the IRB will be included. Copies of all IRB documentation will be forwarded to the FAST-MAG UCLA Central Coordinating Center.
- 10) **Informed Consent:** Blank copies of the IRB-approved Informed Consent form(s) will be filed in this section. The site nurse coordinator will give the patient a copy of the Informed Consent. The original, signed Informed Consent form will be kept in the patient's Case Report Form notebook. Copies can also be maintained in the patient's medical chart.
- 11) **Site Investigator Contact List:** All versions of the Site Investigator Contact List will be filed in this section. Updated copies will be forward to the FAST-MAG UCLA Central Coordinating Center as they are generated.
- 12) **General Correspondence:** Study correspondence between the FAST-MAG UCLA Central Coordinating Center or the data management center and each site

will be filed this section.

- 13) **Serious Adverse Event Reports:** All communications containing information on serious and/or unexpected events will be filed in this section.
- 14) **IND Safety Reports:** All reports received from the FAST-MAG UCLA Central Coordinating Center will be filed in this section.
- 15) **Clinical Supplies:** Completed versions of the site tools will be filed in this section.

7.4.3 Updating and Retention of Regulatory Documents

The central study monitor will review the contents of the regulatory documents binder at each site at each interim monitoring visit and notify the site principal investigator and the site nurse coordinator of any omissions or out of date documents.

Each site must retain all CRFs, supporting documentation and administrative records for:

- A minimum of two years after notification of FDA approval of magnesium for the indication of stroke, or
- A minimum of 2 years after trial completion if no application is filed and the US FDA and the applicable national and local health authorities are notified.

8. Statistical Design and Analysis Plan

All analyses will be executed on the intent-to-treat population, which will consist of all randomized patients grouped by how they were randomized. All statistical tests will be conducted at the 0.05 level of significance. SAS will be used to perform the statistical analyses and to generate the tables and data listings.

8.1 Baseline Characteristics

Baseline characteristics will be compared between the two treatment groups to assess covariate balance. Wilcoxon Rank-Sum tests will be used for continuous variables; Fisher's exact tests and Chi-Square tests will be used for grouped or categorical variables.

8.2 Primary Study Endpoint

8.2.1 Primary Study Efficacy Analysis

The primary objective of this study is to determine if treatment with magnesium sulfate improves the long-term functional outcome of hyperacute stroke patients. The primary endpoint that will be examined will be modified Rankin Scale scores assessed 3 months poststroke. Data will be analyzed to test the null hypothesis that the distribution of scores on the modified Rankin Scale at Day 90 is identical in the magnesium sulfate and placebo groups, versus the one-sided alternative that the distribution of scores is shifted lower in the active magnesium sulfate therapy group. The statistic used to test the primary hypothesis will be the Cochran-Mantel-Haenszel test statistic performed on the rank scores and stratified by transport vehicle. The criterion for statistical significance will be set at an alpha level of 0.05.

The rank based Cochran-Mantel-Haenszel test is designed to test against the alternative that there is a uniform shift of size "delta" in the Rankin score distribution from one group to the other after stratification by other factors. We will compare the two cumulative distribution functions (CDFs) and carry out the Conover procedure to determine if this alternative is reasonable. [16] If not, we will consider more robust test procedures such as the Kolmogorov-Smirnov (K-S) test. The K-S procedure is also rank-based and tests against a general alternative to the null hypothesis instead of a more restrictive delta shift alternative.

8.2.2 Exploratory Secondary Efficacy Analyses of the Primary Study Endpoint

Pretreatment demographic and clinical variables, such as age, sex, time between symptom onset and drug administration, pretreatment LAMS score, pretreatment GCS score, premorbid Rankin score, past stroke, and medical history items, will be considered as possible predictors of treatment effect or confounders that could mask the treatment effect. Non-discrete covariates will be categorized for inclusion in the statistical model. Where evidence of a differential treatment effect or masking exists, appropriate strata will be incorporated and a Cochran Mantel Haenszel's test will be used to test the primary outcome while controlling for the identified variable. Breslow-Day's test will be used to test the consistency of effect across the strata at alpha level of 0.1. The pretreatment demographic and clinical variables that are potential covariates will be considered for inclusion in a logistic regression analysis of the dichotomized Rankin Scale (≤ 2).

Planned subgroup analyses will analyze outcomes on the primary endpoint among patients with ischemic stroke; patients with intracerebral hemorrhage; patients with ischemic stroke treated with conventional intravenous tissue plasminogen activator; patients with ischemic stroke not treated with conventional intravenous tissue plasminogen activator; patients with stroke treated within 60 minutes of onset; and patients with stroke treated between 61-120 minutes of onset. These analyses will be performed in a similar manner to the primary analysis. In addition, planned exploratory analyses will analyze outcomes on the primary endpoint among male and female subgroups and among Census-recognized ethnic and racial subgroups.

8.3 Secondary Efficacy and Safety Endpoints

Secondary endpoints include the Barthel Index of Activities of Daily Living, the National Institute of Health Stroke Scale (neurologic deficit), the Stroke Impact Scale (stroke-specific quality of life), Glasgow Outcome Scale (global outcome). The difference between the treatment groups in the distribution of the scores on these scales will be analyzed by the Wilcoxon Rank-Sum Test at the alpha level of 0.05. No formal corrections will be made for multiple comparisons, as these analyses will be regarded and labeled as exploratory.

The percentage of patients with excellent positive outcomes and good positive outcomes on the BI, mRS, NIHSS, and GOS will be analyzed, with excellent outcomes defined as Rankin ≤ 1 , BI ≥ 95 , NIHSS ≤ 1 , GOS =1, and good outcomes as BI ≥ 60 , NIHSS ≤ 8 , and GOS ≤ 2 . These dichotomized outcomes will be analyzed using Pearson's chi-squared test for independence at the alpha level of 0.05.

Treatment group comparisons of the incidence of mortality will be analyzed using Pearson's chi-squared test for independence.

8.4 Missing Data

The modified Rankin Scale assigns a worst outcome score, 6, to deceased individuals, obviating the need for separate adjustments to the primary analysis to handle death as an outcome.

For the BI, NIHSS, GOS, and SIS, missing 90-day endpoint values will be replaced with the worst case value if the patient died, e.g. BI = 0, INIHSS=42, GOS = 5. If the patient did not die, patients with data from a visit after day 7 but missing data on day 90 will be analyzed employing the last observation carried forward (LOCF). Patients with no data available from any visit after day 7 will have worst-case values assigned for the day 90 datapoint, e.g.

BI = 0, NIHSS = 42, GOS = 5.

8.4.1 Interim Analyses

To ensure that appropriate ethical consideration is given to the welfare of the patients enrolled in the study, NINDS-NIH has appointed a Data and Safety Monitoring Board (DSMB). The DSMB will review the incidences and circumstances of adverse events that occur during the course of the trial. Formal interim analyses will occur after 25%, 50%, and 75% of patients have been enrolled. The objectives of the DSMB are ordered as follows:

1. To monitor the safety of the study subjects.
2. To recommend stopping the trial due to futility.
3. To recommend stopping the trial due to overwhelming efficacy.

An *efficacy* interim analysis will test the null hypothesis that the distribution of scores on the modified Rankin Scale at Day 90 is identical in the magnesium sulfate and placebo groups versus the one-sided alternative that the distribution of scores is shifted lower in the active magnesium sulfate therapy group. This test will be performed at the 1% alpha level at each interim analysis. This is the same null hypothesis employed in the final primary trial efficacy analysis (evaluating whether patients are benefitted by treatment with magnesium sulfate), and will enter into the Lan and DeMets spending function.

A *safety* interim analysis will test the null hypothesis that the distribution of scores on the modified Rankin Scale at Day 90 is identical in the magnesium sulfate and placebo groups versus the one-sided alternative that the distribution of scores is shifted lower in the control placebo therapy group. This test will be performed at the 1% alpha level at each interim analysis. This analysis will be conducted to ensure that patients are not being harmed by assignment to the magnesium sulfate group during the course of the trial. As this pure safety, one-sided analysis does not overlap with the final efficacy analysis (evaluating whether patients are benefitted by treatment with magnesium sulfate), it will not enter into the Lan-DeMets spending function.

Futility analysis will be conducted at the three interim analyses, calculating the conditional probability of a positive result on the primary efficacy outcome based on the observed treatment effect in the the data collected to that point. If the probability of a positive outcome is below 10%, the DSMB may recommend study termination due to futility.

8.5 Sample Size

Sample size calculations project that 95% of enrollees will have acute cerebrovascular disease, including 80% with acute cerebral ischemia and 15% with acute intracerebral hemorrhage, and assume that magnesium sulfate will alter outcome among patients with acute cerebral ischemia and will not alter outcomes among patients with final diagnosis of intracerebral hemorrhage or nonstroke. Sample size calculations also take into account the three planned interim data analyses. Distribution of modified Rankin Scale scores in the placebo group at 3 months was estimated based on observations in the placebo groups of the < 3 hour NINDS-TPA trials, the < 3 hour lubeluzole trial (J. Grotta, personal communication, 9/01) and the < 3 hour CLASS-T trial (P. Lyden, personal communication, 9/01). Distribution of modified Rankin Scale scores at 3 months in the magnesium sulfate group (effect size) was projected at approximately 70% of the effect size observed in Muir's meta-analysis of 4 phase 2 randomized

controlled trials of magnesium for focal stroke, a conservative projection given the long treatment window employed in these trials.

It was projected that this effect size would vary among three groups of patients.

- 1) In patients with ischemic stroke not treated with TPA, the effect size was set at that derived from the magnesium sulfate phase 2 trials.
- 2) In patients with ischemic stroke treated with TPA, the effect size would be modified by two factors: a) better outcome in placebo treated patients due to the administration of TPA, and b) lesser effect size of magnesium sulfate as some tissue at risk would already be salvaged by TPA. For TPA treated patients, distribution of modified Rankin Scale scores at 3 months in the FAST-MAG placebo group were based on observations from the NINDS-TPA. Treatment effect size was anticipated to be 80% of the effect seen in non-TPA treated patients, and varied in sensitivity analysis from 65% to 100%. This is a conservative estimate as concomitant therapy with TPA could actually magnify rather than attenuate magnesium sulfate effects on tissue salvage, for example by increasing delivery of magnesium to penumbral tissues. The proportion of enrolled patients treated with TPA was anticipated to be 20%, and varied in sensitivity analysis from 10 to 35%.
- 3) In patients with intracranial hemorrhage and in patients with final nonstroke diagnoses, the effect size was set at nil.

The power to detect the treatment effect in 1298 patients (649 in each arm) in the intent-to-treat population is 80%.

The assumed treatment effect size is highly clinically significant. The effect size is based on the entire distribution of the modified Rankin Scale, but is somewhat analogous to a 6% improvement in the proportion of patients achieving final modified Rankin Scale scores ≤ 2 . Most stroke experts, when intuiting the minimal clinically important treatment effect around which acute stroke neuroprotective trials should be designed, suggest an absolute effect of 5-10% as a [17,18] More formal analysis, employing the Stroke Policy Model (based, in turn, on Framingham Study data) suggests that absolute treatment effects in improving outcome from acute stroke of 2-4% on the Rankin Scale are clinically meaningful. [18]

9. Approaches to Potential Difficulties

9.1 Recruitment

Achieving planned rates of patient recruitment is frequently a challenge in acute stroke trials. This could particularly be a challenge for the proposed study, which has a briefer time window for patient enrollment than any previous phase 3 acute stroke trial. Therefore, we have carefully designed the trial to encompass the entire Los Angeles County region to ensure that recruiting targets can be met in a timely fashion.

The trial will draw on a large population base. The population of Los Angeles County is 9.8 million. As a result, Los Angeles County is larger than 42 states in the nation. The 69 hospitals in the County that will participate in this trial admitted 14,076 stroke patients in 1999 (data from the California State OSHPD). The planned trial sample size of 1270 thus represents 3.0% of the stroke admissions that will occur to trial hospitals during the study timeframe, a highly achievable proportion. The NINDS TPA trials, using a similar time window to our study (3 hours post CT is approximately equivalent to 2 hours pre CT), recruited 4% of screened patients. If FAST-MAG recruits at the same 4% rate, the trial will be completed more than 1 year earlier than planned. The 424 patients per year enrollment rate countywide translates to a

local enrollment rate of 6 patients per hospital per year, or about than one patient every other month per participating hospital.

Our experience in the FAST-MAG Pilot Trial additionally supports the feasibility of the planned enrollment schedule. At a single receiving hospital, under 2 hour patients were enrolled at a rate of ~10 per year. If enrollment countywide in the main trial occurs at this rate, the trial again will be completed more than 1 year earlier than planned.

To ensure that potential study patients are being identified and offered enrollment in the trial, study coordinators will review all radio calls to their base station hospitals. Any calls in which the diagnosis of stroke was made will be reviewed to determine whether the patient was offered enrollment in the study. Patients appropriate for the study who are not enrolled will be reviewed by Dr. Starkman (chief Emergency Physician Investigator) and the physician-director of the salient EMS service. Feedback will be given to personnel involved in these call to determine reasons for non-enrollment and correct any problems regarding the protocol.

The diversity of the languages in the Los Angeles population is a consideration that must be taken into account in planning informed consent for a prehospital trial performed countywide. Hispanics account for 44.6% of the Los Angeles County population according to year 2000 U.S. Census data. Enrolling a high number of Hispanic patients is a goal of the trial. To ensure fully informed consent and substantial enrollment in the Hispanic population, all ambulances will carry consent forms translated into Spanish in addition to English. In addition, the call schedule for physician-investigators who will be consenting patients by phone in the field will be arranged to include at all times a Spanish-speaking as well as an English-speaking investigator.

After English and Spanish, no other primary language is spoken by more than 2% of the Los Angeles population. Accordingly, patients who do not speak English or Spanish will not be enrolled in the trial in its initial phases. The UCLA IRB requires that consent be elicited in the native language of the speaker, and arranging for on-call interpreters for additional languages is not an efficient strategy, given the rarity of non-English, non-Spanish patients. If in the course of the trial it becomes apparent that a substantial number of patients are being missed because they fall in one or more additional language groups, we will make arrangements to expand recruitment to these patients by translating consent forms and recruiting additional physician-investigators in the target language(s).

Should recruitment lag behind targets despite these measures, we are prepared to expand the trial to other sites. Our investigative team has a close collaborative relationship with the prehospital system in adjoining Riverside and Orange Counties, California and could easily expand the trial to these regions. We also have received offers to collaborate from prehospital care systems in Seattle, West Virginia, Florida, and elsewhere, that could be utilized. However, we anticipate no difficulty in completing the study on time in Los Angeles County.

9.2 Potential for Unblinding by Clinically Ordered Serum Magnesium Levels

In the course of ordinary clinical care of acute stroke patients, magnesium serum levels are currently variably obtained at study hospitals. The FAST-MAG Trial will allow magnesium management to follow customary care at each facility. There will not be a requirement that drawing of magnesium levels be avoided or that all drawn magnesium levels be kept blinded and not be entered in hospital information systems. Some patients in the placebo arm may have hypomagnesemia and require supplemental therapy, and suppressing customarily drawn

magnesium levels would impair their diagnosis and treatment.

To ensure that key trial outcome evaluations remain unbiased, it is required that 1 month and 3 month outcome evaluations be performed by non-site FAST-MAG study nurses who have had no previous contact with the patient, the medical record, the case report form, of the treating team. This will make certain that the key outcome data for the primary endpoint and the preponderance of secondary endpoints will be obtained by fully blinded personnel.

9.3 Selection and Analysis of Endpoints

Acute stroke clinical trials have varied widely in choice of the assessment scale for primary endpoint analysis and the statistical method of analyzing this endpoint. The FAST-MAG trial will use the modified Rankin Scale as the primary endpoint. As a global measure of disability, the Rankin Scale offers the most comprehensive measure of functional outcome among the several outcome measures routinely employed in acute stroke trials. For this reason, it has been frequently employed as a primary endpoint in stroke trials and has been adopted by the Cochrane Collaboration as the most important measure for analysis when performing meta-analyses or results across trials. FAST-MAG will additionally collect data on other standard measures of outcome (NIHSS, BI, GOS, mortality) and analyze these in prespecified secondary analyses.

The additional use of a quality of life scale outcome measure will be an important innovation of the FAST-MAG trial. Quality of life scales are sensitive to fine-grained changes in outcome from mild and moderate stroke undetected by other outcome measures. Additionally, standard measures like the modified Rankin Scale and the Barthel Index, assess primarily physical aspects of stroke outcome. Quality of life scales can assess other important dimensions of illness outcome, including emotion, communication, cognition, and social role function. The Stroke Impact Scale is a validated assessment of quality of life specifically in patients with stroke. [12] FAST-MAG will be the first NIH-NINDS funded phase 3 acute stroke trial to include a quality of life measure as a major secondary endpoint.

The method of statistical analysis of the primary endpoint is always a critical issue in acute stroke trials. Most prior trials employing the Rankin Scale and Barthel Scale as primary endpoints have used a dichotomous outcome, dividing the scales at various, somewhat arbitrarily chosen cutoffs. [19] Random chance will cause the ideal cutoff point to vary from one trial to the next. Trials may appear positive if one cutoff is employed and negative if another, as occurred with ECASS II and PROACT II. Moreover, many patients enrolled in the trial will not contribute data to a dichotomized outcome. A treated patient who improves from a Rankin 5 to a Rankin 3 will not contribute to an analysis dichotomized for good outcomes at Rankin ≤ 2 . This will especially be a problem for drugs like neuroprotective agents in which a treatment effect across the full range of outcomes is likely (as opposed to thrombolytics which are likely to improve some patients dramatically and others not at all). When it is expected that the study drug is likely to exert an effect at all levels of stroke severity, the use of all of the data within a categorical scale is the most powerful approach to endpoint analysis. For this reason, chi-square analysis of the distribution of rank scores reflecting outcomes across the entire range of the Rankin Scale is the planned statistical methodology for the primary analysis in FAST-MAG.

9.4 Generalizability

The generalizability of a clinical trial to actual everyday practice settings is always a concern. FAST-MAG is highly generalizable. It will be performed in the Los Angeles County,

a county with the greatest population diversity of any in America, and with wide geographic variation from dense urban core (downtown Los Angeles), to suburban sprawl (San Fernando Valley), to rural settings (Playa Vista, Malibu). The trial will be performed at a wide range of hospital sites, from small to large and community to academic. The prehospital components of FAST-MAG are highly generalizable. The prehospital stroke identification instrument employed in FAST-MAG (LAPSS) is now a component of ACLS training for paramedics nationwide. [20] In many prehospital systems, paramedics are already authorized to give magnesium in the field for other conditions and administration of magnesium is a simple variation upon existing protocols for administering drugs in the field employed by all paramedics.

4.9.5 Training Paramedics in Study-Related Procedures and Maintaining Study-Related Knowledge Base

Since paramedics have the pivotal role in prehospital therapy, it will be essential for us to effectively teach them about the rationale behind the study and the guidelines for patient enrollment and treatment. Having trained all paramedics in the City of Los Angeles in the Los Angeles Prehospital Stroke Screen under a grant from the American Heart Association (PI, M Eckstein), our group already has extensive experience with large-scale education of paramedics in stroke-related care. The adoption of the LAPSS by the Los Angeles City Emergency Medical System as a required form for all stroke runs and for routine paramedic training ensures strong baseline LAPSS-stroke knowledge level among participating paramedics.

Maintaining paramedic expertise in stroke recognition and LAPSS and LAMS employment over the four-year study period will be challenging. This task will be accomplished in several ways. A continuous paramedic education program will be administered throughout the study period by the investigators and nurse coordinator. Paramedics new to the system will undergo LAPSS and LAMS training, employing training and certification videotapes that we developed and successfully employed in the LAPSS prospective validation study. [21] The certification tape consists of 5 video vignettes of paramedics performing the LAPSS/LAMS exam on 3 stroke patients, 1 stroke mimic (alcohol intoxication), and 1 normal. Certification requires correctly scoring all 5 patient vignettes. All paramedics in this study will be required to achieve LAPSS/LAMS certification. Paramedics will complete a LAPSS-based stroke curriculum that we have developed which provides education to prehospital personnel acute stroke pathophysiology, stroke signs, prehospital management and the latest developments in treatment. In addition, for the FAST-MAG trial, we will employ the videotape education production facilities of the Los Angeles City Emergency Medical System to create a training videotape that specifically reviews FAST-MAG trial procedures. After initial training, refresher classes will be given every 3-6 months, and a trial newsletter with paramedic-generated tips and

lessons from trial experience will be mailed to all Los Angeles County paramedics monthly, utilizing the format of the FAST-MAG Pilot Trial newsletter.

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EXHIBIT D
Administrative Requirements

NIH Grants Policy Statement dated 3/01, including addenda in effect at the beginning date of the budget period http://www.nih.gov/grants/policy/nihgps_2001/

45 CFR Part 74

OMB Circular A-110, “Uniform Administrative Requirements for Grants and Agreements with Institutions of Higher Education, Hospitals, and Other Nonprofit Organizations”, as revised; and

OMB Circular A-122, “Cost Principles for Nonprofit Organizations

OMB Circular A-133, “Audits of States, Local Governments, and Non-Profit Organizations”, as revised.

EXHIBIT E

Compliance Requirements

Civil Rights. Compliance with Title VI of the Civil Rights Act of 1964.

Handicapped Individuals. Compliance with Section 504 of the Rehabilitation Act of 1973 as amended.

Sex Discrimination. Compliance with Section 901 of Title IX of the Education Amendments of 1972 as amended.

Age Discrimination. Compliance with the Age Discrimination Act of 1975 as amended.

Drug-Free Workplace. Compliance with the Drug-Free Workplace Act of 1988.

Patents, Licenses, and Inventions. Compliance with the Standard Patent Rights clauses as specified in 37 CFR, Part 401.14 and/or 35 U.S.C. 203, whichever is appropriate and applicable. LA EMS AGENCY shall notify University's Administrative Contact, as stated in Article 22, within two months after Subrecipient's inventor discloses invention(s) either sole or jointly in writing to LA EMS AGENCY's personnel responsible for patent matters. LA EMS AGENCY shall use form HHS568 to report invention(s). A negative report is not required.

Human Subjects. Compliance with the requirements of federal policy (P.L. 93-348) concerning the safe-guarding of the rights and welfare of human subjects who are involved in activities supported by Federal funds.

Use of program income; Add/Deduct Option described in the NIH Grants Policy Statement shall apply.

Debarment and Suspension. LA EMS AGENCY specifically certifies that it is not presently debarred, suspended, proposed for debarment, declared ineligible or voluntarily excluded from covered transactions by any Federal department or agency.

Non-Delinquency on Federal Debt. LA EMS AGENCY specifically certifies that neither it nor any person to be paid from funds under this Agreement is delinquent in repaying any Federal debt as defined by OMB Circular A-129.

Restrictions on Lobbying. Compliance with PL 101-121, Title 31, Section 1352, which prohibits the use of Federally appropriated funds for lobbying in connection with this particular Agreement.

Affirmative action for disabled Veterans and Veterans of the Vietnam era Compliance with Public Laws 92-540 and 93-508, Executive Order 11701, and the regulations of the Secretary of Labor (41 CFR Part 60-250) in promoting employment opportunities for disabled and Vietnam veterans.

Health Insurance Portability and Accountability Act of 1996, Public Law 104-191 (HIPAA): The LA EMS AGENCY certifies that it is familiar with the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and its accompanying regulations, and will comply with all applicable HIPAA requirements in the course of this Agreement

EXHIBIT G, LA EMS AGENCY A-133 CERTIFICATION

The undersigned, being an authorized financial officer of the referenced LA EMS AGENCY, hereby certifies that:

_____ The LA EMS AGENCY’s total Federal expenditures for fiscal year ending _____ do not exceed \$500,000.00. The LA EMS AGENCY is exempt from Federal Audit requirements for the subaward period of performance.

_____ The LA EMS AGENCY has had an A-133 compliance audit for fiscal year ending _____ and has not been informed of any instances of non-compliance with federal laws and regulations that have a direct bearing on this Agreement. A copy of the Subrecipient’s written notification as promulgated in Subpart C, Section.320(e)(2) of OMB Circular A-133 is attached or is available at the following website address:
_____.

_____ The LA EMS AGENCY has had an A-133 compliance audit for fiscal year ending _____ and has been informed of instances of non-compliance with federal laws and regulations that have a direct bearing on this Agreement. Copies of the LA EMS AGENCY’s written notification and reporting package as promulgated in Subpart C, Section.320(E)(1) and (2) of OMB Circular A-133 is attached.

_____ The LA EMS AGENCY has not yet completed an A-133 compliance audit for fiscal year ending _____. The audit is to be completed by _____. A copy of the LA EMS AGENCY’s written notification and, if applicable, the reporting package or website containing the information will be forwarded to UCLA when available.

Signature of Authorized Representative

Date

Printed Name and Title