

Major Kidney Clinical Research Studies and Projects Inventory*

North American IgA Nephropathy Study

1. Administrative Data

(a) Name of study/research project and acronym:

North American IgA Nephropathy Study, A Randomized, Placebo-Controlled, Multicenter Trial Evaluating (a) Alternate-Day Prednisone and (b) Fish Oil Supplements in Young Patients with IgA Nephropathy.

(b) Type of study/research project (randomized clinical trial, epidemiological study, database, etc.):

Randomized clinical trial.

(c) Funding status (currently funded, study/project completed):

Currently funded. Project will be completed February 2003.

(d) Recruitment status (recruitment completed, currently recruiting):

Recruitment completed.

(e) For studies/project currently recruiting: indicate total sample size/ number currently enrolled, anticipated period of recruitment:

Not applicable.

(f) Data coordinating center principal investigator contact information (mailing address, phone, fax, e-mail address):

Ronald J. Hogg, MD
Medical City Dallas Hospital
7777 Forest Lane, C-740
Dallas, Texas 75230
Phone: 972.566.5575
Fax: 972.566.8027
E-mail: spnsg@lonestarhealth.com

(g) Number of recruiting sites, list of principal investigators at recruiting sites, and contact information as in (f) above:

See Appendix A.

(h) List of principal investigators at central laboratories/facilities (identify type of central facility) and contact information as in (f) and (g) above:

Keith Hyland, Ph.D.
HPLC Laboratory
Institute of Metabolic Disease
3812 Elm Street
Dallas, TX 75246
Phone: 214.820.4857
Fax: 214.820.4853

(i) Roster of Data and Safety Monitoring Board/Scientific Advisory Committee or other oversight committee(s):

Data Coordinating Center:

Jeannette Lee, Ph.D.
Biostatistics Unit
University of Alabama at Birmingham
Birmingham, AL

Scientific Planning Committee:

Sharon Andreoli, M.D.	Eileen Brewer, M.D.	Daniel Cattran, M.D.
James Donadio, M.D.	Ronald J. Hogg, M.D.	Keith Hyland, Ph.D.
J. Charles Jennette, M.D.	Bruce Julian, M.D.	Jeannette Lee, Ph.D.
Daniel Savino, M.D.	Richard Sibley, M.D.	Bryson Waldo, M.D.
Robert Wyatt, M.D.		

(j) Private-sector support (type of support—e.g., financial, donation of drugs/placebo, etc.):

Pronova Biocare – donation of drug, OMACOR,[®] and matching placebo
Merck – donation of drug, Vasotec,[®] and matching placebo
Upjohn – donation of drug, prednisone, and matching placebo
Medical City Dallas Hospital – supplemental funding for central office and personnel

2. Study Design (For completed studies, a copy of the primary publication can substitute for information below.)

(a) Objective:

The main purpose of this study is to test the hypothesis that alternate day prednisone or daily fish oil supplements will retard or prevent the decline in renal function expected in children, adolescents, and young adults with moderate to severe IgAN.

(b) Study design:

This study is a placebo-controlled, prospective clinical trial designed to evaluate the efficacy of alternate-day prednisone and fish oil capsules in children, adolescents, and young adults with IgA nephropathy (IgAN) who are at risk of progressive disease. Each patient will receive two years of treatment followed by three years of follow-up off of treatment. Note that ACE inhibitors may also be prescribed at the discretion of the treating physician for normotensive patients in each of the three groups.

(c) Major inclusion criteria:

- Age: patient must be ≤ 40 years at time of evaluation for the study
- GFR: ≥ 50 ml/min/1.73m² based on pre-study measurement of GFR (by local PI)
- Proteinuria: protein excretion >0.5 g/1.73m²/24 hours or urine/protein/creatinine ratio >0.5 on two occasions 1 month or more apart in the six months prior to entry into the study
- A renal biopsy showing IgAN
- Patient must be able to swallow a 500mg OMACOR[®] placebo capsule

(d) Major exclusion criteria:

- Systemic lupus erythematosus
- Henoch-Schönlein purpura
- Abnormal liver function: i.e., AST or bilirubin ≥ 2 X normal or known chronic liver disease
- Pregnancy or unwillingness to use appropriate measures to avoid pregnancy during the study
- Diabetes mellitus, cataracts, aseptic necrosis of any bone, or other conditions potentially exacerbated by prednisone therapy
- Prednisone or other immunosuppression and/or fish oils for more than three months since the time of renal biopsy (If a patient has received one or more of these agents for less than three months, he or she may enter the study if the medication is stopped for one month prior to study entry)

(e) Description of the intervention(s):

Treatments to be compared are as follows:

Group A: Placebo Control Group. This group will be randomized to receive 2 years of treatment with placebo tablets or capsules plus treatment of persistent hypertension with the ACE inhibitor, Enalapril. This will be given to patients who have either a systolic BP>140, a diastolic BP>90, or either level >95th percentile for age on two consecutive visits. If a patient cannot tolerate Enalapril, or if optimal blood pressure control cannot be achieved with the maximum dose of Enalapril, additional anti-hypertensive medication may be prescribed for patients in this group as well as those in Groups B and C below.

Group B: Prednisone Group. This group will receive 2 years of treatment with a tapering regimen of prednisone tablets plus Enalapril in patients with hypertension (as above).

Group C: Fish Oil Capsules Group. This group will receive 2 years of treatment with fish oils plus Enalapril in patients with hypertension (as above). The preparation to be used in this study will be ethyl ester concentrate encapsulated fish oil (OMACOR[®]) capsules and matched placebo (olive oil) capsules.

(f) Baseline/eligibility visit schedule (number of visits, major assessments):

Month 2 screening visit: Informed consent signed after study is described in detail. Patients will be asked to swallow a placebo tablet and capsule before proceeding further. Diagnostic biopsy report sent to the ACC for review by study pathologists. Results of local measurements of glomerular filtration rate (GFR) and protein excretion will be reviewed. Screening evaluation, consent verification, and renal biopsy forms will be sent to ACC to assess patient eligibility.

(g) Follow-up contact schedule (frequency, type of visit-phone, in-clinic, major assessments):

Months 1 and 2: Visits to monitor for toxicity from medication.

Month 3 to month 24: Treatment follow-up visits every 3 months.

Month 27 to month 60: Post-treatment follow-up visits every 3 months.

(h) Primary outcome, secondary outcomes:

The primary outcome criterion will be estimated glomerular filtration rate (GFR), based on serial determinations of true serum creatinine measurements by HPLC. A secondary outcome criterion will be proteinuria.

(i) Brief summary of power estimates used to justify sample size/duration, including critical assumptions (i.e., effect-size estimates, estimated event rates, or rate of change in outcome measure):

Sample size estimation—The null hypothesis is that there is no difference between the three treatment arms with respect to time to failure. The alternative hypothesis is that at

least one of the active treatment arms is superior to placebo in slowing the progression of renal disease. To estimate the sample size required for the study, the following assumptions were made:

- time to failure is exponentially distributed,
- recruitment will occur over two years,
- each patient will be observed for a minimum of 5 years or until failure,
- the dropout rate at 3 years will be 10%; and
- the cumulative proportion of patients who fail at 3 years is estimated as 5% for each of the two active treatment arms (fish oil and steroid therapy) and 20% for placebo.

A sample size of 123, equally divided between the three treatment arms, will be sufficient to compare each active treatment arm against placebo at the Bonferroni adjusted .05 significance level with power of .75.

With 41 patients per treatment arm, a difference in the incidence of adverse events of 25% between each active treatment arm and placebo can be detected at the .05 significance level with power of .66.

(j) Web site:

www.spnsg.org

3. Data and Biological Sample Resources

(a) Biological samples collected in ongoing studies/research projects (specify the type of sample—blood, urine, etc.; the amount; and the point in the study when samples were collected—e.g., baseline visit #1, baseline visit #2, follow-up visit #1; specify months after randomization/study entry):

Blood (10-15 ml) per visit and urine specimens (30 ml per specimen) are obtained on up to 21 occasions in patients who complete the entire five years of study. The timing of the specimens is shown on the Protocol Flow Sheet (Appendix C).

(b) Biological samples currently in storage from completed trials (grid showing sample collection time, type of sample, amount, and number of study participants sample was collected from, and physical location of where the samples are stored):

Some serum specimens are frozen in storage at Medical City Dallas. The actual volumes and time of the specimens are currently being catalogued. Renal biopsy slides have been made on all patients. These will be returned to participating centers when the study results have been analyzed.

(c) Brief summary of typical informed consent provisions (template informed consent form acceptable), including major variables in participant consents, if applicable. For example, “use for

other studies or not”, “allow genetic studies or not.” Does consent include use of samples in other studies that are not part of the main study?

See Appendix B.

(d) Data collected (grid of data collection by time/clinic visit with specificity on the type of information collected—e.g. quality of life with SF-MOS 36, measurement of kidney function by GFR, serum creatinine measurement, etc.):

See Appendix C.

(e) Any provisions for distributing resources outside of the study? What is the sharing plan?

No

4. Ancillary Studies

(a) Process and contact person (name, address, phone, fax, and e mail address) for application to perform ancillary studies:

Ronald J. Hogg, MD
7777 Forest Lane, C-740
Dallas, TX 75230
Phone: 972.566.5575
Fax: 972.566.8027
E-mail: spnsg@lonestarhealth.com

(b) List of ancillary studies approved, completed and ongoing (including source of funding and amount):

None

5. List of Publications and Presentations (full citations, also note manuscripts in progress)

Not applicable.

6. Cooperative Agreement, Contract, and Selected Investigator-Initiated NIDDK Supported Studies*

Sub-contracts were established by Medical City Dallas with all of the centers listed on the attached list of Participating Centers in order to reimburse them for activities related to patient recruitment and follow-up.

Appendix A. North American IgA Nephropathy Study

Participating Centers and Principal Investigators

Center Name/Location	Principal Investigator PN = Pediatric Nephrologist IM = Internal Medicine	Telephone	Fax
Medical City Dallas Hospital 7777 Forest Lane C727 Dallas TX 75230-2518	*Ronald Hogg, M.D. (PN)	972-566-5575	972-566-8027
Children's Hospital of Alabama 1600 Seventh Avenue S CHT 735 Birmingham AL 35233	Bryson Waldo, M.D. (PN) Bruce Julian, M.D. (IN)	205-939-9781 205-934-9045	205-975-7051 205-934-7742
Texas Children's Hospital 6621 Fannin, #800 MC3-2482 Houston TX 77030-2399	Eileen Brewer, M.D. (PN) Wadi Suki, M.D. (IN)	713-770-3800 713-790-3275	713-770-3889 713-790-5053
Stanford University Medical Ctr. Division of Nephrology, S201 Stanford, CA 94305-5114	Richard Layfayette, M.D. (IN) Steve Alexander, M.D. (PN)	650-723-6247	650-723-7917
Cook Children's Hospital 801 Seventh Street Ft Worth TX 76104	Watson Arnold, M.D. (PN)	817-885-4260	817-885-3943
Arkansas Children's Hospital 800 Marshall Street, Slot 512 Little Rock AR 72202	Eileen Ellis, M.D. (PN)	501-320-1847	501-320-3551
University of Colorado Health Science Center 4200 East 9th Avenue Box A-036 Denver CO 80262	Doug Ford, M.D. (PN) Isaac Teitelbaum, M.D. (IN)	303-861-6263 303-315-6713	303-764-8156 303-315-4852
University of Tennessee 50 N. Dunlap, Room 301 Memphis, TN 38103	Robert Wyatt, M.D. (PN) Kim H. Huch, M.D. (IN)	901-572-5366 901-523-8990	901-572-5036 901-577-7487
University of Texas Health Science Center at San Antonio Department of Pediatrics 7703 Floyd Curl Drive San Antonio TX 78284	Ihsan Elshihabi, M.D. (PN)	210-567-5279	210-358-4764
University of Texas Medical Branch Child Health Center Room C2.21 03703 Galveston, TX 77550	Steven Diven, M.D. (PN)	409-772-2538	409-772-5293
University of Texas Health Science Center at Houston P.O. Box 20708 Houston, TX 77225 (643 Fannin, MSB3124 Houston, TX 77030)	Ronald J. Portman, M.D. (PN) Thomas DuBose, M.D. (IN)	713-500-5675 713-500-6873	713-500-5680 713-500-6882
University of Chicago 5841 S. Maryland M Code 6051 Chicago IL 60637	Andrew J. Aronson, M.D. (PN) Fredric Coe, M.D. (IN)	773-702-6412 773-702-1473	773-702-2488 773-702-5818

Kidney Disease Clinical Studies Initiative, Major Kidney Clinical Research Studies and Projects
Inventory,* North American IgA Nephropathy Study

Johns Hopkins School of Medicine 600 N. Wolfe Street, Park 327 Baltimore MD 21287	*Barbara Fivush, M.D. (PN)	410-955-2467	410-614-3680
Schneider Children's Hospital 271-16 76th Avenue, Rm 365 New Hyde Park, NY 11042	*Howard Trachtman, M.D. (PN) Pravin Singhal, M.D. (IN)	718-470-3491 718-470-7360	718-470-0887
University of Kentucky Medical Ctr. Department of Pediatrics Kentucky Clinic Bldg. J459 Lexington KY 40536	Beth Jackson, M.D. (PN) Peter Sawaya, M.D. (IN) Richard Baehler, M.D. (IN)	606-323-6033 606-323-5048 606-276-5355	606-257-7706 606-323-1020 606-275-1630
Queen's Physician Office Bldg. 1380 Lusitania, #808 Honolulu, HI 96813	James Musgrave, M.D. (PN)	808-521-3473	808-521-3474
Loma Linda University Medical Ctr. Dept. of Pediatrics 11175 Campus Street Room A113D Coleman Pavillion Loma Linda CA 92354	Shobha Sahney-Long, M.D. (PN)	909-824-0800 X42212	909-824-4184
Children's Mercy Hospital Nephrology Section 2401 Gillham Road Kansas City MO 64108	Bradley A. Warady, M.D. (PN)	816-234-3010	816-234-3494
Children's Hospital Medical Ctr. 333 Burnet Avenue Cincinnati, OH 45229-3039	Thomas Welch, M.D. (PN) John Galla, M.D. (IN)	513-559-4531 513-558-5471	513-636-7407 513-558-4309
Cardinal Glennon Memorial Hospital 1465 S. Grand Boulevard St. Louis, MO 63104	Ellen Wood, M.. (PN)	314-577-5662	314-268-6459
Children's Hospital and Medical Ctr. P.O. Box 5371/CH-46 Seattle, WA 98105	Sandra Watkins, M.D. (PN) Richard Johnson, M.D. (IN)	206-526-2524 206-543-3792	206-528-2636 206-685-8661
Children's National Medical Ctr. 111 Michigan Avenue, NW Washington, DC 20010	Kanwal Kher, M.D. (PN)	202-884-5058	202-884-3621
Children's Hospital of Buffalo 219 Bryant Street Buffalo NY 14222	James Springate, M.D. (PN)	716-878-7275	716-888-3801
Mayo Clinic MNCG S24 200 First SW Rochester, MN 55905	Timothy Larson, M.D. (IN) Bruce Morgenstern, M.D. (PN)	507-266-1047 507-284-6415	507-266-7891 507-266-7891
University of North Carolina Campus Box 7155 347 MacNider Building Chapel Hill, NC 27599-7155	Ron Falk, M.D. (IN)	919-966-2561	919-966-4251
University of Iowa College of Medicine 200 Hawkins Dr, 2861 JPP Iowa City, IA 52242-1083	Craig C. Porter, M.D. (PN) John A Bertolatus, M.D. (IN)	319-356-3988 319-356-8225	319-384-9616 319-356-2999

Kidney Disease Clinical Studies Initiative, Major Kidney Clinical Research Studies and Projects
Inventory,* North American IgA Nephropathy Study

Rhode Island Hospital 593 Eddy Street Providence, RI 02903	Lance Dworkin, M.D. (IN)	401-444-5253	401-444-8453
University of Florida P.O. Box 100296 Gainesville FL 32610-0296	Robert Fennell, M.D. (PN)	352-392-4434	352-392-7107
LSU Medical Center Children's Hospital Pediatric Nephrology 200 Henry Clay Avenue New Orleans, LA 70118-2822	Matti Vehaskari, M.D. (PN)	504-896-9238	504-896-9762
The Nemours Children's Clinic 83 West Columbia Street Orlando, FL 32806-1101	Jorge Ramirez, M.D. (PN)	407-650-7240	407-650-7244
University of Rochester Department of Pediatrics 601 Elmwood Avenue, Box 777 Rochester, NY 14642	Melissa Gregory, M.D. (PN)	716-275-9784	716-756-8054
University of Michigan C.S. Mott Children's Hospital Mott F6865/Box 0297 1505 Simpson Road East Ann Arbor, MI 48109-0297 800-962-3555	Timothy Bunchman, M.. (PN) Sean Leavey, M.D. (IM)	734-936-4210 734-764-3157	734-763-6997 734-763-0982
St. Elizabeth's Medical Center 736 Cambridge Street Boston, MA 02135-2997	James Strom, M.D.	617.789.2588	617.789.2036
Carolina's Medical Center Department of Pediatrics P.O. Box 32861 Charlotte, NC 28232-2861	Susan Massengill, M.D. (PN)	704-355-4292	704-355-5429
Gunderson Lutheran Medical Foundation 1836 South Avenue La Crosse, Wisconsin 54601-5494	Fadi Ghandour, M.D.	608.782.7300	608.791.4488
Toronto Hospital C.C.R.W. 3-884 101 College Street Toronto, Ontario, Canada M5G 1L7	Daniel Cattran, M.D. (IN)	416-340-4187	416-340-3714

Appendix B. North American IgA Nephropathy Study

Participation Explanation and Consent Form

Project Title: A Randomized, Placebo-Controlled, Multicenter Trial Evaluating A) Alternate-Day Prednisone and B) Fish Oil Supplements in Children and Young Adults with IgA Nephropathy

Sponsor: National Institutes of Health

Investigators:

Telephone No.:

Participant:

(Last) (First) (MI)

Address: _____

Phone No.: _____

BACKGROUND INFORMATION:

IgA nephropathy is a disease of the kidneys which leads to loss of blood and protein in the urine and can lead to severe kidney failure even when it begins in childhood. Unfortunately, there is no proven treatment for IgA nephropathy, although a few reports have described the successful treatment of patients with this condition with either fish oil supplements or a medication called prednisone. Although the results of these studies are too few to allow final conclusions, they do suggest that the treatments are usually not associated with significant side effects.

I understand that I am being asked to participate in a 5-year research study which will compare every-other-day prednisone or daily fish oil capsules with a placebo (a pill which contains no medicine) in the treatment of my IgA nephropathy. I have been asked to join this study because a biopsy of my kidney showed that I have a fairly severe degree of IgA nephropathy, which is likely to cause more severe kidney disease in the future if no treatment is given. I will be randomized by lot (or chance) to take either prednisone, fish oil supplement or placebo, and neither I nor the investigator will know which treatment I will receive.

PROCEDURES (WHAT WILL HAPPEN TO ME DURING THIS STUDY)

I understand that if I wish to participate in this study, I will have a complete medical examination and some blood and urine tests before I can receive any treatment. If these tests show that my kidney function is within the limits set by the study protocol, I will return to the clinic and be given a 3-month supply of prednisone, fish oil capsules or placebo. Neither the doctor nor I will know which I am taking. However, if at any time this information becomes medically necessary, it will be available to my doctor. I will also be given a medication called Enalapril (Vasotec) if my blood pressure is found to be high. This is a standard medicine for the treatment of high blood pressure. My doctor will adjust the dose until my blood pressure is in the normal range for my age. I will report to the clinic for an examination and blood tests after 1, 2, and 3 months of study and then every three months until I have been followed for 5 years. The dosage of medication may be decreased after the 3-month and 12-month visits and may be adjusted according to my weight if this changes significantly. It will be stopped after the 24-month visit. I understand that the investigator may stop my participation in the study if he believes it is in my best interests to do so. If my kidney function falls by approximately one-third, I will be taken out of the study and treatment with other drugs may be offered. Hospitalization will not be necessary for this study. I will not be paid for taking part. Although I will not be charged for the cost of the drugs or kidney function tests (which will be provided by a grant from the National Institutes of Health), I will be responsible for charges for my routine medical care.

RISKS THAT MAY OCCUR DURING THE STUDY

Prednisone can cause high blood sugar (diabetes), bone disease, high blood pressure, cataracts, poor growth and reduce my resistance to some infections. It is very unusual for these side effects to occur in persons given the prednisone every other day, although unexpected (adverse) effects may occur. More frequent side effects include mild swelling of the face, increase in weight, acne, depression, and increase in mood swings. There may be possible pain and a small bruise at the site of the needle puncture for the blood draw.

If I develop high blood pressure and therefore given Enalapril (Vasotec) to control my blood pressure, the following complications may be seen: headache, dizziness, diarrhea, decrease in kidney function, cough, low blood sugar, rash, difficulty in sleeping, muscle cramps, loss of taste and a lowering of white blood cells. These are not seen in most patients but I understand that I should call the doctor if they occur when I am being treated with this drug.

Fish oil supplements have no significant side effects at the doses used in this study but may leave a bad taste in my mouth.

No female who may be pregnant should join the study, since prednisone and Enalapril may damage a developing fetus. If there is even a possibility of pregnancy at the time of entry or at any other time during the study, a pregnancy test must be performed.

Appendix C. North American IgA Nephropathy Study

Protocol Flow Sheet

Visit month #	Screen-2	Pre-Entry-1	Entry 0	1,2	3,9,15,21	6,18	12	24	27,33,39,45,51,57	30,42,54	36,48	60
Consent Form	X											
Clinical Data Review	X											
Renal Biopsy Review	X											
Height	X	X		X	X	X	X	X	X	X	X	X
Weight	X			X	X	X	X	X	X	X	X	X
Blood Pressure	X	X		X	X	X	X	X	X	X	X	X
Physical Exam	X	X		X	X	X	X	X	X	X	X	X
Urinalysis	X	X		X	X	X	X	X	X	X	X	X
Adverse Events Form				X	X	X	X	X	X	X	X	X
Medication Dispensed			X		X	X	X					
Med Vials Returned					X	X	X	X				
Instruction Booklet			X									
<i>To Lab Corp:</i>												
Urine Protein		X				X	X	X		X	X	X
HPLC Se Creat for Est GFR		X			X	X	X	X	X	X	X	X
CBC		X				X	X	X		X	X	X
Chemistry Profile		X		X	X	X	X	X	X	X	X	X
ANA		X										X