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The North American Fetal Therapy Network (NAFTNet): a new approach to collaborative research in fetal diagnosis and therapy

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S U M M A R Y

In August 2004, the National Institutes of Health organized a 'Workshop on Fetal Therapy' to develop a plan for the maternal–fetal, surgical, and neonatal evaluation and treatment of pregnancies that might benefit from in-utero therapy. At the completion of the workshop several recommendations were made, foremost of which was the 'formation of a cooperative group of clinical investigators to help set a national agenda for research and clinical progress in the field of fetal therapy'. Somewhat by coincidence, a multidisciplinary 'Fetal Therapy Working Group' that had been formed earlier in the year was well-positioned to accept this national mandate and proposed development of a North American Fetal Therapy Network (NAFTNet) to foster collaborative research between active fetal diagnosis and treatment centers in both the USA and Canada, develop a peer review mechanism for study proposals, explore ways to centralize data collection and study development, and establish an educational agenda for medical professionals and the public as well as training of future leaders in the field. NAFTNet represents a new paradigm and approach to international collaborative research. Early success has resulted in the recognition of the power of collaborative research efforts in studying rare congenital anomalies and intervention strategies to improve outcomes and survivals in such limited populations. By abandoning 'competitive research' for a cooperative, collaborative environment of research partnership, NAFTNet strives to be more responsible and effective in using limited resources and improving care for pregnancies and children born with congenital anomalies.

1. Introduction

At the Society of Maternal Fetal Medicine (SMFM) meeting in January of 2004 a 'spirited discussion' occurred over the future of fetal therapy and who should take the lead to promote and drive development of the field. It was recognized that the pattern of practice was one of competition for patients, given the limited number of anomalies prenatally diagnosed each year, and with each center trying to gain expertise in managing these uncommon anomalies. Unfortunately, this approach resulted in limited patient populations such that each of the existent fetal diagnosis and therapy centers only saw a small portion of the patients diagnosed each year. Therefore, it took significantly longer to generate sufficient numbers of patients to develop clinically significant natural history information and understanding of how in-utero interventions affect outcomes. Also, new programs were emerging that were further diluting the small patient populations with specific anomalies that might benefit from in-utero therapy. By the end of the evening, all participants were in agreement that a new era of cooperative, collaborative research was necessary if the field of fetal diagnosis and therapy was to move forward in concert with technological advances in the field.

The participants in this discussion from the University of California – San Francisco (UCSF), the Children's Hospital of Philadelphia (CHOP), Vanderbilt University Medical Center, and University of North Carolina – Chapel Hill, represented the majority of the comprehensive fetal surgery programs in the USA, and these programs formed a 'Fetal Therapy Working Group' to facilitate collaborative research between these four centers. These institutions were drawn together by a mutual interest in the in-utero repair of spina bifida and under the leadership of Dr Harrison at UCSF had succeeded in achieving funding for the first multicenter randomized trial of a maternal–fetal intervention (MOMS trial). Through the remainder of the 2004 SMFM meeting, members of the working group (Dr Robert Ball, UCSF; Dr Mark Johnson, CHOP; Dr Nancy Chesheir, Vanderbilt; Drs Anthony Johnson and Ken Moise, Chapel Hill) continued to meet to move this idea forward. During these discussions, the importance of inclusiveness led to

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recognition of an underlying need for a national collaborative network to capture rare anomalies, the need to expand participation (develop a 'net'work to capture as many of these rare cases as possible), the need for patient and physician education about these rare anomalies, the need for centralized data collection and management, and the responsibility to train future generations of fetal interventionalists. Members of this group agreed to continue to work on the design and implementation of this new idea.

Somewhat by coincidence, the National Institutes of Health (NIH) also recognized the emerging field of fetal diagnosis and therapy and organized a 'Workshop on Fetal Therapy' in August of 2004. This workshop brought together a world-class group of experts to discuss the history of developments, current status of investigations in the field, future directions and needs, issues of maternal and fetal safety and ethical aspects of research in this area. The goals of this workshop were to develop a plan for the maternal–fetal, surgical, and neonatal assessment of pregnancies that might benefit from in-utero therapy, and the need for appropriate mechanisms for dissemination of innovations to improve patient care and infant outcomes. Several areas of importance were discussed that included the role of animal studies, important lessons learned from previous clinical trials, problems with recruitment given the limited number of cases identified each year, how to pay for such studies, the impact of rapidly evolving technology, and how to successfully complete studies and randomized trials. Other questions addressed included the definition and measure 'success', and how to assure appropriate informed consent for these vulnerable patients.[1]

At the end of the workshop several recommendations were made, foremost of which was the 'formation of a cooperative group of clinical investigators to help set a national agenda for research and clinical progress in the field of fetal therapy'. To be successful, such a group would need to emphasize ethical issues, protect maternal and fetal health, develop and enforce clinical standards for research centers, and work with insurance payers and funding agencies to support clinical research and trials. They noted that to be effective, such a group would need to solidify collaborative agreements to pool and triage patients with specific disorders, develop a process for peer review of research proposals by experts in the field to provide credibility and protection for research centers to gain Institutional Review Board (IRB) approval and participate in studies, and help develop a national infrastructure in the areas of data collection, training of study coordinators, and establishment of consistent outcome measures and research standards. Unfortunately, these recommendations did not come with any offer for government financial support.

Following completion of the NIH-sponsored Workshop, the Fetal Therapy Working Group was already well-positioned to accept this national mandate and proposed development of a North American Fetal Therapy Network (NAFTNet) to foster collaborative research between the more active fetal diagnosis and treatment centers in both the USA and Canada. In October of 2004, they met to determine the overall design of the network, address the administrative and financial aspects, scientific review and oversight of active collaborative studies, and mechanisms for the development of infrastructural support in the areas of membership and education based on existing collaborative research models. By the end of the meeting, the decision was made to create an Executive Committee (EC) to serve as the administrative arm of the network to address issues of overall organizational and infrastructure development, financial support, development of administrative policy and oversight, and function as a disciplinary body if necessary. A Steering Committee (SC) was also proposed that would serve as the scientific arm of the network whose primary responsibility was the peer review of proposed study protocols, scientific oversight and monitoring of ongoing studies and participation on subcommittees formed by the EC to help with membership, publication guidelines, and educational materials for both the public and medical communities. With this agreement began the process of developing a formal Charter for the organization, whose official mission is: 'providing a cooperative clinical research network to study the natural history of fetal disease, develop therapeutic prenatal interventions to improve outcomes, function as an educational resource for patients and healthcare providers, and train future leaders in clinical and basic science research in the field of fetal intervention'.

Conference calls preceeded the second meeting in April 2005, and defined the composition, terms of service, and administrative responsibilities of the EC, an operating budget was proposed, and each of the founding Centers on the EC committed to pay annual dues to cover the operating expenses of the organization. Also, a detailed description of the composition of the SC, terms of service, member responsibilities, and a process for scientific review of study proposals was defined.

To assure multidisciplinary representation the Organizing Committee was expanded to include Dr Michael Harrison (pediatric surgery from UCSF), Dr N. Scott Adzick (pediatric surgery from CHOP), Dr William Walsh (neonatology from Vanderbilt), as well as two non-voting ad-hoc members representing study development and biostatistics (Dr Elizabeth Thom, Georgetown University) and bioethics (Dr Frank Chervenak, Cornell University).

In October 2005, 13 centers as well as a representative of the NIH/NNational Institute of Child Health and Human Development (NICHD) were invited to an organizational meeting where the mission, organizational structure, committee responsibilities and requirements for member participation were presented. From the 13 centers invited, 12 accepted the invitation to join the organization as the founding members of the SC, officers were elected for the committees, and responsibilities for all members as defined in the Charter were accepted (Box 1). Since then, four additional Centers have become members, bringing SC membership to twenty as established in the Charter (Montreal Children's Hospital & CHU Sainte-Justine Research Center, Texas Children's Hospital & Baylor Medical Center – Houston, Magee Women's Hospital – University of Pittsburgh Medical Center, and University of Texas Southwestern Medical Center – Dallas) (Fig. 1).

2. Annual reporting of center's experience

To help investigators develop research proposals using pooled potential patient populations for recruitment to achieve adequate power to increase the success of a study, all NAFTNet member centers are required to submit a detailed annual report of the number of cases seen with anomaly-specific diagnoses and the number of specific fetal interventions performed within their Center. These data are submitted anonymously through the NAFTNet website (www.naftnet.org), reviewed by the Chair of the EC to screen for mistakes or inconsistencies (validate data integrity), and then the data from all centers are posted as a composite total on the web site representing the combined experience of NAFTNet. For example, while one individual center may evaluate 10–12 cases of gastroschisis a year, the whole of NAFTNet saw 231 such cases in 2007, therefore providing access to patient populations that allow more opportunity for recruitment and successful completion of studies in a reasonable period of time.

3. Process for peer review of study proposals

For peer review and oversight purposes, a staged process was established. To illustrate the process, we will consider a study

Box 1. Founding NAFTNet membership

Executive Committee
Mark Johnson MD (Chair), Obstetrics/Genetics, Children's Hospital of Philadelphia
Robert Ball MD (Vice Chair), MFM, Univ. California – San Francisco
Anthony Johnson DO (Secretary), MFM/Genetics, Univ. N. Carolina – Chapel Hill
Nancy Chescheir MD (Treasurer), MFM, Vanderbilt University Medical Center
Michael Harrison MD, Pediatric Surgery, Univ. California – San Francisco
Kenneth Moise MD, MFM, Univ. N. Carolina – Chapel Hill
N. Scott Adzick MD, Pediatric Surgery, Children's Hospital of Philadelphia
William Walsh MD, Neonatology, Vanderbilt University Medical Center
Christopher Harman MD (Steering Committee Chair), MFM, Univ. Maryland

Purpose
- provide administrative support
- amend bylaws and Charter as needed
- promote mission through website development
- oversight of Steering Committee activities
- set annual dues and membership requirements
- develop and maintain data management systems
- maintain guidelines for study submission
- initial screening of concept proposals
- identify outside funding support
- educational development
- administer disciplinary actions

Steering Committee
Christopher Harman MD (Chair), MFM, University of Maryland Medical Center
Joshua Copel MD, MFM, Yale University Medical Center
Timothy Crombleholme MD, Cincinnati Children's Hospital – Pediatric Surgery
Alain Gagnon MD, MFM, Univ. British Columbia – Vancouver
Garrett Lam MD, MFM, Phoenix Perinatal Associates
Hanmin Lee MD, Pediatric Surgery, University of California – San Francisco
Francois Luks MD, Pediatric Surgery, Brown University Medical Center
Giancarlo Mari MD, MFM, Wayne State University – Detroit
Kenneth Moise MD, MFM, University N. Carolina – Chapel Hill
Richard O'Shaughnessy MD, MFM Ohio State University Medical Center
Greg Ryan MD, MFM, University of Toronto
Ronald Wapner MD, MFM/Genetics, Columbia University Medical Center – NYC
R. Douglas Wilson MD, MFM/Genetics, Children's Hospital of Philadelphia
Martin Walker MD, MFM, Evergreen Medical Center – Seattle
Louise Wilkins-Haug MD, MFM, Brigham & Women's Hospital – Boston
Edmund Yang MD, Pediatric Surgery Vanderbilt University Medical Center
Frank Chervenak MD, Cornell University Medical Center – NYC (ad hoc advisor: Ethics)
Catherine Spong MD, MFM (ad hoc NIH/NICHD advisor)
Elizabeth Thom PhD, Georgetown University – Washington, DC (ad hoc advisor: Biostatistics/Study Design)

Purpose
- review research proposals
- mentoring support for proposal revisions
- oversight committee for ongoing studies
- advisory committee for principle investigator (PI) with funded studies
- participation in appointed subcommittees
  - membership development
  - data management
  - website development/management
  - education and training

comparing traditional vesicoamniotic shunt placement compared with in-utero fetoscopic laser resection of posterior urethral valves for management of lower urinary tract obstruction (LUTO). To help with study design, the principle investigator (PI) principle investigator (Current NAFTNet Member Centers. would go to the NAFTNet website to look at the annual composite database to evaluate the number of potential cases available for recruitment through the Network to use for study design, power analysis and whether the project can realistically be completed with the available study population or whether recruitment may also need to occur outside of NAFTNet as well. For example, at the PI's Center, they may see four or five cases of LUTO each year. However, between all twenty NAFTNet Centers, the PI would see that 131 and 114 cases were diagnosed in 2006 and 2007 respectively. The PI would then submit a Concept Proposal to the EC. The Concept Proposal is a two to three page outline of the primary hypothesis and research question, brief

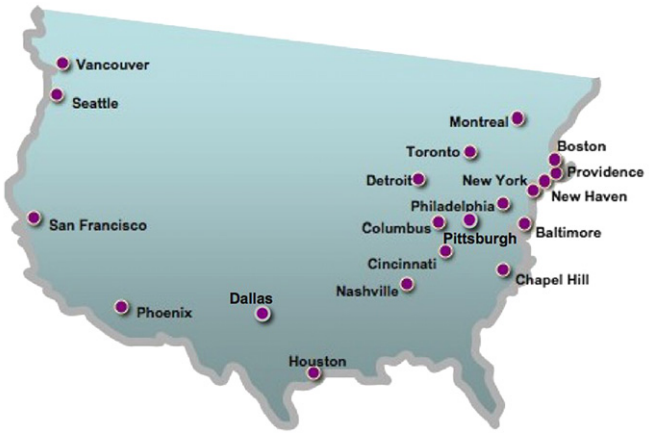

Fig. 1. Current NAFTNet Member Centers.

background of the problem, description of methods, proposed timeline for study, maternal and fetal risk assessments, plans for long-term follow-up, and whether specialized reviewers for the study are recommended. If the EC determines by majority vote that the proposal is consistent with the NAFTNet mission, the EC Chair provides the PI with a summary of the questions and concerns raised by the EC members to address prior to their SC presentation.

The PI then submits a more detailed study proposal of seven to eight pages to include a discussion of budget and potential funding resources to the Chair of the SC 30 days prior to the next NAFTNet meeting. The Chair reviews the full study proposal and assigns two SC members based on related expertise to formally review and critique the study at the next meeting. The PI presents the study to the SC that is followed by comments from the assigned reviewers and then opened for discussion concerning strengths, weaknesses, important questions to address, and whether the study can realistically be completed as proposed. If the study is approved to move forward but with recommendations for revisions, the SC Chair provides the PI with a summary of issues raised at the initial review and open discussion. The PI will then have the opportunity for follow-up presentation during which they identify where revisions were made and address the questions raised at the initial presentation. If approved, all NAFTNet member Centers who have the resources and patient population appropriate to the study are obligated to obtain local IRB approval and participate in the study or refer patients to other NAFTNet Centers who can. The PI will also receive a letter indicating NAFTNet's combined Center commitment to the study to help the PI with application for grant or outside funding. The PI can then use this letter of support to demonstrate to funding agencies their access to larger patient populations, additional support and oversight of their study, and greater likelihood of being able to successfully complete the study in a reasonable time period. Alternatively, the PI can request 'fast track status' for their study if they already have funding or are in application for funding and feel that obtaining NAFTNet support will significantly strengthen their application. Following initial presentation, a two-thirds majority vote would be required for approval, and the PI would receive the same notification of support from the organization and will be required to provide study updates to the SC at each of the annual meetings.

4. Incorporation

Given the self-funded status of the organization, a mandate was put forward by the EC to pursue 501(c) status as a not-for-profit organization to facilitate contributions from outside organizations, individuals, and industry to support the mission and reduce the financial burden for participating member centers. In January 2007, 501(c) status was granted, with the members of the EC now also serving as the Board of Directors for the organization and the elected EC Chair, Secretary and Treasurer assuming these responsibilities within the corporation as well.

5. Education

To address the mission of public and healthcare professional education, NAFTNet members voted to fund development of a web site (www.naftnet.org, www.naftnet.com) where information about prenatal diagnosis and fetal interventions would be posted for the public and healthcare professionals. In addition, a password-protected members' side of the website was created containing links to the composite annual Center data experience from each year, as well as required annual administrative forms, a listing of all active NAFTNet sites including the names and contact information for each center, a listing of all active NAFTNet studies including the ability to download the protocol, data forms, study specific instructions for local PIs, and a standardized sample consent document and IRB submission forms to help each member center with their IRB submissions. In addition, the website members' side has the capacity to allow data entry into study-specific databases as well as posting of password-limited information to members of the EC and SC. Non-members can gain access to the public side of the website by simply registering on the website, following which they will receive their login information by e-mail.

6. Membership

Present membership is restricted to the EC and SC member Centers. However, a general membership category is being developed that would include annual dues to support growth and development of the organization, to provide general members access to the member side of the website to view active study protocols for potential patient referral or participation in some studies, to respond to general discussion topics, to register to attend the SC/scientific meeting as an observer, and to apply for any openings in the SC. General members may also be asked to serve on special topic committees requested by the EC, and may also submit study proposals for consideration through sponsorship of a sitting SC Center.

Terms of general membership are open and renewable annually. Steering Committee membership is presently set at 20 members by the Charter, and members must meet specific qualifications demonstrating their activity in prenatal diagnosis, various forms of prenatal therapy, and access to appropriate internal and IRB review and oversight. Terms are three years, and are renewable by the EC based on whether the Center wishes to continue to serve, and their participation and fulfillment of responsibilities specified in the Charter. The SC elects a Chair to serve a three-year term as their representative on the EC. The EC is chosen from members of the SC who serve three-year terms. Beginning in 2008, three members of the Founding EC began to rotate off the committee in a phased manner each year to allow new individuals to participate in the administrative branch of the organization, with each Center having equal opportunity to do so by annual election.

SC Centers designate a principal member who agrees to attend the majority of all twice annual meetings. However, each Center is allowed to designate an alternate that can attend the meetings as a non-voting participant, to learn the committee process and be able to represent their Center if the principal member cannot attend. Members of the EC can also serve as their Center's principal

or alternate member on the SC. Such rules were established to help maintain continuity in leadership and memory of ongoing issues and process within the organization.

7. Recent successes

NAFTNet presently has eight approved research studies that are actively enrolling patients (Box 2). One study has NIH funding and another study is funded by industry.

In January 2009 at the SMFM, our first completed collaborative study, 'Radiofrequency ablation for twin-reversed arterial perfusion sequence (TRAP)', was presented in the opening Plenary Session. NAFTNet members have also assumed an active leadership role in organizing and running the Special Interest Group on Fetal Surgery at the SMFM meetings.

Perhaps one of our most significant contributions in the area of education was the organization and primary sponsorship of an International Consensus Conference on the Management of Quintero Stage I Twin–Twin Transfusion Syndrome (TTTS) held prior to the start of the SMFM meeting.

The principal organizer and investigator for a proposed international collaborative study to assess whether selective laser photocoagulation therapy could further improve long-term survivals and decrease neurodevelopmental morbidity if performed earlier in the TTTS process (Stage I) approached NAFTNet to participate in this treatment trial. The proposed treatment trial was formally presented and discussed at the October 2008 meeting that concluded there was very little published about the natural history and outcomes in untreated Stage I disease, or Stage I cases treated with amnioreduction or selective laser photocoagulation, and it was unclear whether sufficient equipoise existed within the scientific community to justify a randomized treatment trial at this time. A recommendation to organize and financially support a consensus conference on the management of Stage I TTTS disease was approved and an organizational committee was quickly formed. Following the NIH guidelines for consensus conference development, a draft program was developed and the Organizing Committee realized that the upcoming SMFM meeting offered a unique opportunity to have representatives from the major fetal treatment centers from around the world present in one place at one time. By coordinating the consensus conference with the SMFM meeting, a robust discussion among individuals active in research and with treatment experience in early TTTS disease may determine whether an international collaborative treatment trial for Stage I disease was justified at this time. An Expert Panel was constituted to listen to presentations from invited speakers and listen to the open discussion, and then ask questions in three primary areas: (1) Has recent research advanced our understanding of the pathophysiology of TTTS sufficiently that we should consider revising the original Quintero Staging System for TTTS from 1999? (2) What do we know about the natural history of untreated Stage I TTTS, and how have various treatments for more advanced stages (II–IV) altered survival and neurodevelopmental outcomes? (3) What has been the clinical experience to date in use of selective laser in Stage I disease, and what are the ethical considerations when determining equipoise for such studies based on present information? The charge to the Expert Panel was to consider the information and discussion of the day and develop a summary statement and recommendation in each of these three areas. The summary statement will be submitted for publication in Summer 2009 to help guide future research in this area as well as help develop health care policy for management and treatment of TTTS by government policymakers and grant agencies as well as health insurance providers.

8. Summary

NAFTNet represents a new paradigm and approach to international collaborative research in the field of fetal diagnosis and therapy. Early success has resulted in the recognition of the power of such collaborative research efforts in studying rare congenital anomalies and intervention strategies to improve outcomes and survivals in such limited populations. By adopting a collaborative environment of research partnership, NAFTNet strives to be more effective in using limited resources and improving care for pregnancies and children born with congenital anomalies. The interest and will for success is strong, as demonstrated by the present self-support within our organization's institutions. The future success of more complicated treatment trials will, however, require additional resources from the health care community, insurance providers as well as government and private granting agencies. Without such financial support, this unique opportunity for advancement will undoubtedly merge with the frustrations of the past and present for these families.

Acknowledgements

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Box 2. Active NAFTNet research studies

1. Oxidative stress in fetuses with decompensated alloimmune hemolytic disease of the fetus and newborn (HDFN).
2. Natural history registry for pregnancies complicated by prenatally diagnosed lower urinary tract obstruction (LUTO) with normal amniotic fluid volume.
3. Role of lung area/head circumference ratio, magnetic resonance imaging and fetal echocardiography in predicting outcome in prenatally diagnosed congenital diaphragmatic hernia.
4. Radiofrequency ablation for twin-reversed perfusion sequence (TRAP).
5. Predictive biologic markers in twin-to-twin transfusion syndrome.
6. Prenatal cytogenetic diagnosis by array-based copy number analysis.
7. Determination of the accuracy of free fetal DNA in maternal plasma in the assessment of the fetal RhD blood type.
8. Twin-to-twin transfusion syndrome pregnancies after selective laser therapy: prediction of fetal/neonatal death.

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Conflict of interest statement

None declared.

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Reference

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