

## **SETTLEMENT AGREEMENT**

### **I. PARTIES**

This Settlement Agreement (“Agreement”) is entered into between the United States of America, acting through the United States Department of Justice and on behalf of the Center for Biologics Evaluation and Research (“CBER”) of the Food and Drug Administration (“FDA”), the National Institutes of Health (“NIH”), the Office of Acquisition Management and Policy of the Department of Health and Human Services (“HHS”), and the Office of Inspector General (“OIG-HHS”) of the Department of Health and Human Services (“HHS”) (collectively the “United States”); and Mark L. Batshaw, M.D. (“Dr. Batshaw”) and Children’s National Medical Center (“CNMC”) (hereafter referred to as “the Parties”), through their authorized representatives.

### **II. PREAMBLE**

As a preamble to this Agreement, the Parties agree to the following:

A. The settlement arises out of Dr. Batshaw’s and CNMC’s participation in the development of an investigational new drug to treat a certain deficiency in an enzyme called ornithine transcarbamylase (OTC). The urea cycle, located in the liver, detoxifies nitrogen and changes it to urea which is nontoxic and can then be excreted as urine. Some individuals are unable to convert nitrogen (ammonia) to urea because they are born with deficient or absent activity of OTC, an essential enzyme for making urea. A high level of ammonia is toxic to the central nervous system and as a result, hyperammonaemic coma and death may occur with OTC deficiency (OTCD).

B. A Phase I safety study of the use of a genetically engineered adenovirus being inserted into human research participants to address OTCD was reviewed by the FDA and NIH. The OTC gene was placed inside a virus called adenovirus and the virus was injected into the liver

through blood vessels. The virus then carried the OTC gene into the subject's liver cells and once in the liver cells, the OTC gene was to produce the OTC enzyme that is missing in OTCD. The studies of the safety of this drug in humans were regulated by the FDA. The research studies were funded by the NIH and by the FDA.

C. Dr. Batshaw is a licensed physician who specializes in pediatrics and metabolic disorders. He is currently the Chief Academic Officer at CNMC. During all relevant times pertaining to this settlement, Dr. Batshaw was Principal Investigator on the grant issued by the National Institutes of Health, National Institute of Child Health and Human Development (Grant Number P01 HD32649), entitled "Recombinant Adenovirus Gene Transfer In Adults With Partial Ornithine Transcarbamylase Deficiency." Dr. Batshaw became Principal Investigator on the Investigational New Drug Application (IND) as of March 1998. Dr. Batshaw was also a sub-investigator on the FDA grant.

D. Children's National Medical Center (CNMC) was part of a collaborative effort with the Institute for Human Gene Therapy at the University of Pennsylvania on the NIH OTC grant and received federal funds.

E. The United States contends that it has certain civil claims against CNMC and Dr. Batshaw as a result of his actions, as an employee of CNMC, in his study of this new investigational drug described in paragraphs A-D above between July 1998 through September 1999: false statements and claims in connection with the submission of grant applications, progress reports, and annual reports to, and receipt of federal funds from, the NIH; false statements and claims in connection with submissions to the FDA; false statements and claims in connection with the failure to obtain properly informed consent from human research participants; and false statements made

to Institutional Review Boards charged with oversight of this research. In addition, the allegations contained in the November 30, 2000 warning letter issued by the FDA are incorporated herein by reference. The United States' contentions described above are hereinafter referred to as the "Covered Conduct."

F. Dr. Batshaw and CNMC, as participants in the aforementioned studies, deny that they engaged in any unlawful activity as set forth in Paragraph E above, and to the contrary, contend that their conduct was at all times in good faith, lawful and appropriate.

G. In order to avoid the delay, uncertainty, inconvenience and expense of protracted litigation of these claims and any related regulatory proceedings, the Parties reach a full and final settlement as set forth below.

#### **TERMS AND CONDITIONS**

NOW, THEREFORE, in consideration of the mutual promises, covenants, and obligations set forth below, and for good and valuable consideration as stated herein, the Parties agree as follows:

1. CNMC agrees to pay to the United States the sum of Five Hundred Fourteen Thousand Six Hundred and Twenty-Two Dollars (\$514,622.00) (the "Settlement Amount"). CNMC agrees to make payment of the Settlement Amount by electronic funds transfer pursuant to written instructions to be provided by the Office of the United States Attorney, within thirty (30) days of the final execution of this Agreement.

2. Dr. Batshaw agrees that knowledge of and compliance with all federal laws and regulations governing human clinical research is essential to ensuring the safety of participants in clinical research. To that end, Dr. Batshaw completed training courses and performed other

remedial efforts as more fully set forth in Exhibit 1, which is attached hereto and incorporated herein. Dr. Batshaw further agrees that he will attend, on an annual basis, at least two (2) educational programs sponsored by or conducted by organizations with recognized expertise in the area of clinical research (i.e., enhancing clinical trials and complying with FDA and NIH regulations) during the term of this Agreement. Dr. Batshaw shall provide a certification to the government that he has successfully completed the program within 30 days of completion. To the extent that Dr. Batshaw consults with the FDA and/or NIH and obtains prior approval of his participation in a program, the United States shall be bound by such approval.

3. The Parties recognize that institutional oversight of clinical research, through Institutional Review Boards (IRBs), is critical to ensuring the accurate reporting of data to the government as well as providing protection to participants in clinical research. To that end, CNMC has taken steps to enhance the IRB system oversight of clinical research as set forth in Exhibit 1.

4. The Parties agree that CNMC has retained, with the consent of the United States, an appropriately qualified medical monitor to review Dr. Batshaw's performance in all noninfrastructure clinical research projects regardless of Dr. Batshaw's role in the research. For purposes of this Agreement, "noninfrastructure clinical research project" means NIH/FDA funded and/or regulated research that are individual investigator initiated and focused on a specific clinical research project (e.g. RO1, PO1, U54). Infrastructure grants are defined as providing core facilities or training for more general institutional activities (e.g. General Clinical Research Center, Mental Retardation Research Center, Child Health Research Center Development Award, T32 Postdoctoral training grant). The United States will evaluate the need for a medical monitor on a case by case basis after consultation with Dr. Batshaw and CNMC. The role of the medical monitor is set forth

in Exhibit 1. The medical monitor requirement shall be deemed to have commenced as of October 1, 2004.

5. In recognition of the need to protect human research participants, CNMC has hired a Research Subject Advocate (RSA) to oversee the safety of children participating in clinical trials. The duties and responsibilities of the RSA are outlined in Exhibit 1, section I(B)(4)(e)(4).

6. The Parties agree that CNMC shall employ a research administrator or a Clinical Research Organization (CRO) to oversee the regulatory compliance of all noninfrastructure clinical research projects in which Dr. Batshaw is participating in any capacity. The duties of the research administrator or CRO are set forth in Exhibit 1 attached hereto and incorporated herein. The United States will evaluate the need for a research administrator or CRO on a case by case basis after consultation with Dr. Batshaw and CNMC. Within 30 days of the consultation, the United States will advise Dr. Batshaw and CNMC of its decision regarding the need for a research administrator or CRO for the research project. The CRO requirement shall be deemed to have commenced as of October 1, 2004.

7. For a three year period, Dr. Batshaw and CNMC agree to certify to FDA and the NIH, on an annual basis from the date of execution of this Agreement, that they are in compliance with the terms of this Agreement. The certifications shall be sent to the following addresses:

To the FDA:

Director  
Office of Compliance and Biologics Quality  
Center for Biologics Evaluation and Research  
United States Food and Drug Administration  
1401 Rockville Pike Suite 200N  
Rockville, MD 20852-1448

To the NIH:

Director, Division of Grants Compliance and Oversight  
Office of Policy for Extramural Research Administration  
National Institutes of Health, DHHS  
6705 Rockledge Drive, Suite 350  
Bethesda, MD 20892-7974

8. Dr. Batshaw's name will be added to the list of restricted clinical investigators, currently entitled "Restricted List for Clinical Investigators," which is published on FDA's website. The government agrees that, once Dr. Batshaw fulfills all of the terms of the Agreement, the government will remove Dr. Batshaw's name from the Restricted List for Clinical Investigators and place it on the "Clinical Investigators-Restrictions Removed" website list. Dr. Batshaw acknowledges that, once Dr. Batshaw fulfills all of the terms of the Agreement, information relating to this Agreement, including the fact that the restrictions have been removed, will continue to be publicly available in accordance with freedom of information laws and FDA's policies and procedures regarding public information.

9. Subject to the exceptions in Paragraph 10 below, in consideration of the obligations of Dr. Batshaw and CNMC set forth in this Agreement, conditioned upon CNMC's payment in full of the Settlement Amount, the United States (on behalf of itself, its officers, agents, agencies and departments) agrees to release Dr. Batshaw, CNMC, and Children's Research Institute (CRI), a subsidiary of CNMC, from any civil or administrative claim the United States has or may have under the False Claims Act, 31 U.S.C. §§ 3729-3733; the Program Fraud Civil Remedies Act,

31 U.S.C. §§ 3801-3812; or the common law theories of payment by mistake, unjust enrichment, breach of contract and fraud, for the Covered Conduct.

10. In consideration of the obligations of Dr. Batshaw and CNMC set forth in this Agreement, and conditioned upon CNMC's payment in full of the Settlement Amount as set forth in paragraph 1, HHS agrees to release and refrain from instituting, directing or maintaining any disqualification, debarment, or administrative claim under 21 CFR Part 58, 45 CFR Part 76 or 48 CFR Part 9.4 against Dr. Batshaw and CNMC for the Covered Conduct. HHS also agrees that this settlement does not constitute a civil judgment or a present civil charge pursuant to the NIH Grants Policy Statement and 45 CFR Part 76. Nothing in this Paragraph precludes HHS from taking action against entities or persons, or for conduct and practices, for which claims have been reserved in Paragraph 11 below.

11. Notwithstanding any term of this Agreement, specifically reserved and excluded from the scope and terms of this Agreement as to any entity or person are any and all of the following:

- (a) Any civil, criminal or administrative claims arising under Title 26, U.S. Code (Internal Revenue Code);
- (b) Any criminal liability;
- (c) Except as explicitly stated in this Agreement, any administrative liability, including mandatory exclusion from Federal health care programs;
- (d) Any liability to the United States (or its agencies) for any conduct other than the Covered Conduct;

(e) Any claims based upon such obligations as are created by this Agreement, including those created by Exhibit 1 attached hereto;

(f) Any civil or administrative claims against individuals other than Dr. Batshaw.

12. In the event that Dr. Batshaw or CNMC fails to comply in good faith with any of the terms of this Agreement, or should any of Dr. Batshaw's or CNMC's representations or warranties be materially false, the United States may, at its sole discretion, exercise one or more of the following rights:

(a) seek specific performance of this Agreement and the prevailing party shall be entitled to an award of reasonable attorneys fees and costs in its favor; or

(b) exercise any other right granted by law.

13. Dr. Batshaw and CNMC waive and will not assert any defenses they may have to any criminal prosecution or administrative action relating to the Covered Conduct, which defenses may be based in whole or in part on a contention that, under the Double Jeopardy Clause in the Fifth Amendment of the Constitution, or under the Excessive Fines Clause in the Eighth Amendment of the Constitution, this Agreement bars a remedy sought in such criminal prosecution or administrative action. This settlement is not punitive or penalty in purpose. Nothing in this paragraph or any other provision of this Agreement constitutes an agreement by the United States concerning the characterization of the Settlement Amount for purposes of the Internal Revenue Laws, Title 26 of the United States Code.

14. Dr. Batshaw and CNMC fully and finally release the United States, its agencies, employees, servants, and agents from any claims (including attorneys fees, costs, and



expenses of every kind and however denominated) which they have asserted, could have asserted, or may assert in the future against the United States, its agencies, employees, servants, and agents, related to the Covered Conduct and the United States' investigation and prosecution thereof.

15. The Settlement Amount that CNMC must pay pursuant to this Agreement by electronic wire transfer pursuant to Paragraph 1 above, will not be decreased as a result of the denial of claims for payment to the extent, if any, that such claims are now being withheld from payment by any federal grant program or payer, related to the Covered Conduct; and agrees not to cost transfer any claims from grants related to the Covered Conduct, and CNMC agrees not to appeal any such denials of claims.

16. Dr. Batshaw and CNMC agree that all costs (as defined in 45 C.F.R. § 74.27, 45 C.F.R. Part 74 and 45 C.F.R. Part 92), whether direct or indirect incurred by or on behalf of Dr. Batshaw and CNMC or their agents, employees, or former employees in connection with: (a) the matters covered by this Agreement; (b) the Government's audit(s) and civil and any criminal investigation(s) of the matters covered by this Agreement; (c) Dr. Batshaw and CNMC's investigation, defense, and corrective actions undertaken in response to the Government's audit(s) and civil and any criminal investigation(s) in connection with the matters covered by this Agreement (including attorney's fees), (d) the negotiation of this Agreement, and (e) the payment made pursuant to this Agreement, are unallowable costs under the cost principles applicable to government grants, contracts, cooperative agreements, and other agreements to which 45 C.F.R. Part 74 and 45 C.F.R. Part 92 applies (hereafter, "unallowable costs"). These unallowable costs will be separately estimated and accounted for by CNMC and CNMC will not charge such unallowable costs directly or indirectly to any grants, contracts, cooperative agreements, or other agreements with the United

States or seek payment for such unallowable costs through any cost report, cost statement, information statement or payment request submitted by CNMC or any of its departments or agencies. The parties agree that nothing in this Agreement shall constitute a waiver of any rights the United States may have under 45 C.F.R. § 74.27, 45 C.F.R. Part 74 and 45 C.F.R. Part 92.

17. This Agreement is intended to be for the benefit of the Parties only, and by this instrument the Parties do not release any claims against any other person or entity.

18. CNMC expressly warrants that it has reviewed its financial situation and that it currently is solvent within the meaning of 11 U.S.C. § 547(b)(3), and will remain solvent following its payment to the United States hereunder. Further, the Parties expressly warrant that, in evaluating whether to execute this Agreement, the Parties (i) have intended that the mutual promises, covenants and obligations set forth herein constitute a contemporaneous exchange for new value given to, within the meaning of 11 U.S.C. § 547(c)(1), and (ii) have concluded that these mutual promises, covenants and obligations do, in fact, constitute such a contemporaneous exchange.

19. Each party to this Agreement will bear its own legal and other costs incurred in connection with this matter, including the preparation and performance of this Agreement.

20. Dr. Batshaw and CNMC represent that this Agreement is freely and voluntarily entered into without any degree of duress or compulsion whatsoever.

21. This Agreement is governed by the laws of the United States. The Parties agree that the exclusive jurisdiction and venue for any dispute arising between and among the Parties

under this Agreement will be the United States District Court for the Eastern District of Pennsylvania.

22. This Agreement constitutes the complete agreement between the Parties. This Agreement may not be amended except by written consent of the Parties.

23. The undersigned individuals signing this Agreement on behalf of CNMC and Dr. Batshaw represent and warrant that they are authorized to execute this Agreement. The undersigned United States signatories represent that they are signing this Agreement in their official capacities and that they are authorized to execute this Agreement.

24. This Agreement may be executed in counterparts, each of which constitutes an original and all of which constitute one and the same agreement.

25. This Agreement is effective on the date of signature of the last signatory to the Agreement.

26. All Parties consent to the United States' disclosure of this Agreement, and information about this Agreement, to the public.

THE UNITED STATES OF AMERICA

PATRICK L. MEEHAN  
United States Attorney  
Eastern District of Pennsylvania

DATED: \_\_\_\_\_

BY: \_\_\_\_\_

JAMES G. SHEEHAN  
Associate United States Attorney  
United States Attorney's Office  
Eastern District of Pennsylvania

DATED: \_\_\_\_\_

BY: \_\_\_\_\_

DAVID R. HOFFMAN  
Assistant United States Attorney  
Eastern District of Pennsylvania

DATED: \_\_\_\_\_

BY: \_\_\_\_\_

LEWIS MORRIS  
Chief Counsel  
Office of Inspector General  
United States Department of  
Health and Human Services

DATED: \_\_\_\_\_

BY: \_\_\_\_\_

MARC R. WEISMAN  
Director, Acquisition and Management Policy  
United States Department of  
Health and Human Services

FOR MARK L. BATSHAW, M.D.

DATED: \_\_\_\_\_

BY: \_\_\_\_\_

FOR CHILDREN'S NATIONAL MEDICAL  
CENTER:

DATED: \_\_\_\_\_

BY: \_\_\_\_\_

DATED: \_\_\_\_\_

BY: \_\_\_\_\_

CHARLES A. DE MONACO, ESQ.  
DICKIE, MCCAMEY & CHILCOTE, P.C.

## EXHIBIT 1

### I. DR. BATSHAW'S REMEDIAL EFFORTS

#### A. Dr. Batshaw's Remedial Efforts Following OTCD Gene Transfer Study

1. Remediation:
  - a. On November 30, 2000, FDA issued a warning letter to Dr. Batshaw relating to the OTCD study. As a result, Dr. Batshaw ceased acting as Principal Investigator for any clinical research regulated or funded by the FDA or NIH. Dr. Batshaw responded to the FDA warning letter on December 19, 2000, wherein he proposed corrective actions. On October 11, 2001, FDA advised Dr. Batshaw, "based on the information available at this time, your proposed corrective actions appear to be adequate." During this period of time, the National Institute of Child Health and Human Development administratively withheld funding for two major new center grants where Dr. Batshaw was the proposed Principal Investigator. Dr. Batshaw subsequently received permission to transfer the direction of these grants to other investigators during this period.
  - b. Retrained as a clinical investigator.
  - c. Audited NIH Clinical Research Center course: *Introduction to the Principles and Practices of Clinical Research (IPPCR)*.
  - d. Completed other courses related to training of clinical investigations in the protection of human research participants:
    - (1) Investigator 101 "*Protection of Human Subjects*" new training requirements for all clinical investigators, study coordinators and IRB members, including a compact disk course titled OHRP *Course Investigator 101 "Doing It Right... Together."*
    - (2) CNMC videotape IRB course, titled *Protection of Human Subjects*. (September 2000)
2. Enhancement of Human Research Protection at CNMC:
  - a. Presented FDA warning issues and lessons learned to IRB and ethics forum at CNMC.

- b. In his role as Chief Academic Officer at CNMC and Director of CRI, significantly increased financial and staff support for IRB at CNMC.
  - c. Arranged for voluntary audit of CNMC's IRB by the federal Office of Human Research Protection (OHRP).
  - d. Obtained a NIH grant (K12) to enhance clinical research training of junior investigators at CNMC.
3. External Sharing of Lessons Learned through Public Lectures:
- a. Grand rounds at CNMC, Johns Hopkins Medical Institutions and Harvard Medical School.
  - b. General Clinical Research Center national meeting.
  - c. Society for Inherited Metabolic Disorders national meeting.
  - d. International meeting on inborn errors of metabolism.

**B. CNMC's Remedial Efforts Following OTCD Gene Transfer Study:**

- 1. IRB Audit Committee review of Protocol 2432 and issuance of findings and recommendations.
- 2. Parallel review by external Blue Ribbon Committee.
- 3. IRB Audit Committee recommendations:
  - a. Clarification on strengthening of standards for review of off-site research participation:
    - (1) Development of policies and procedures identifying need for CNMC IRB review.
    - (2) Provision of education for IRB staff/members, investigators, and research staff regarding these policies.
    - (3) As appropriate, formation of inter-institutional "agreements" (with the involvement of IRB's at two sites) to eliminate potential confusion, redundancies, gaps, and contradictory findings.
  - b. Increased attention paid to high risk or complex protocols:



- (1) Increase scrutiny within the IRB.
    - (2) Consideration of outside monitoring as appropriate.
    - (3) Strengthening of staff training within the IRB to promote recognition and appropriate response to high risk or complex protocols.
  - c. Assurance that consent is properly inclusive and appropriately updated:
    - (1) Consideration of inclusion of animal maximum tolerated dose (MTD) results.
    - (2) Consideration of indirect communications between investigators and potential participants outside of the formal consent process.
    - (3) Assurance that risks and benefits in consents are appropriately updated as required by new scientific information and/or adverse event reporting.
    - (4) Requesting and documentation of full financial disclosure regarding potential conflicts of interest that could compromise investigator scientific integrity.
  - d. Identifying and undertaking broader improvements in the IRB to assure the protection of human research participants:
    - (1) Updating IRB policies and procedures at regular intervals.
    - (2) Providing education for faculty members, investigators, research staff, and IRB staff/members.
    - (3) Providing appropriate financial resources for increased IRB volume.
4. Implementation of recommendations:
  - a. Participation in outside research:
    - (1) On-going education has been provided for faculty members, IRB staff/members, research staff regarding the need for

CNMC/CRI IRB review if an investigator is participating in research at another institution.

- (2) Standard operating procedures (SOPs) have been created.
- (3) “Authorization Agreements” with Georgetown University Medical Center, George Washington University School of Medicine and Health Sciences and Howard University Hospital are now in place.
- (4) There is active review and audit of IRB protocols involving participation of CNMC investigators in outside research.

b. IRB policies and procedures have been improved:

- (1) Policies and procedures were updated in May 2002.
- (2) Linked policies and forms are available on the CNMC Intranet website with appropriate menus alerting investigators to appropriate responses and policies.
- (3) SOPs have been created and are regularly updated.
- (4) Information obtained from IRB reviews and audits is provided as feedback to the IRB, its staff, and members so that there are on-going experiences and opportunities for learning that will inform future IRB policies and practices.

c. Specific, improved policies and procedures have been implemented:

- (1) High risk research undergoes augmented review, including submission of adequately comprehensive risk/benefit information derived from the medical literature, outside consultants, etc. as well as review by a designated “High Risk” IRB committee.
- (2) A special IRB with appropriate expertise has been created for evaluation of cancer and HIV research protocols. This ensures a group of reviewers who are familiar with risk/benefits issues, standards for consent, and special circumstances of the studies (e.g. offering palliative care as an alternative to participation in research).

- (3) Risk/benefit disclosure has been strengthened with greater attention paid to the need for appropriate updating of consents as information becomes available in the medical literature or from serious adverse events reporting.
  - (4) Conflict of interest and financial interest disclosures are now required of all investigators.
  - (5) The IRB has developed and implemented an audit/quality improvement process that reviews both randomly selected and targeted protocols.
  - (6) A voluntary quality assurance review was conducted by OHRP on July 31 and August 1, 2002: Over a period of 2-3 days, extensive IRB written materials were reviewed. An on-site review was also conducted. OHRP review staff interviewed IRB staff, research faculty, and CNMC/CRI leadership. The review included a follow-up consultation on October 15, 2002 during which findings and recommendations were presented.
- d. Education in the protection of human research participants has been strengthened:
- (1) Mandatory education is now required prior to obtaining IRB review or participating in research:
    - (a) All investigators, research staff (including data collecting research assistants, study nurses, and project coordinators), IRB staff, and IRB members must document such education.
    - (b) Two courses are required, each with an examination that must be passed successfully.
    - (c) New clinical research fellows are oriented to human research participants protection and IRB requirements during a two-week workshop every July at the beginning of their training.
    - (d) An additional HIPAA course is being developed.
  - (2) In collaboration with George Washington University School of Medicine and Health Sciences, NIH grant support was

obtained by CNMC for an IRB educator (2002-2004) who provides IRB staff training, IRB member education, and a faculty lecture series on human research participants protection.

- (3) IRB member education has been a topic of specific attention. These educational efforts have included:
    - (a) A retreat of the IRB to discuss broad issues related to the protection of human research participants.
    - (b) Members are provided with a textbook that describes the history of the development of federal regulations pertinent to the protection of human research participants, and in relationship to the functioning of an IRB.
    - (c) Each IRB meeting includes a review and discussion of recent OHRP findings, with special attention paid to what can be learned from newly identified deficiencies in the protection of human research participants at other institutions.
    - (d) Each IRB meeting also includes distribution of educational materials, such as recent medical literature pertinent to the protection of human research participants.
  - (4) The CNMC/CRI IRB chair (Dr. John Sever) was certified as an *IRB Professional* as soon as this certification became available in November 2002.
  - (5) Certification of the IRB staff is planned for the coming year.
- e. Resources and support for the IRB have been increased:
- (1) IRB staff (in addition to the Medical Director) has been doubled, from 2 to 5, including an Administrative Director.
  - (2) Increased financial support has been provided to the IRB, with a 50% increase in budget between 2001-2004. In addition, \$150,000 has been allocated by CNMC for the purchase of a web-based IRB review system this year.

- (3) In addition to the other IRB staff, a registered nurse (RN) Quality Improvement Coordinator, who has extensive experience in the conduct of research and human research participants protection, was hired in 2003. She was the former nurse manager of the General Clinical Research Center (GCRC) at CNMC. Her roles include assisting the IRB Audit Committee and staffing the High Risk Research Review Committee
  
- (4) A new Research Subject Advocate (RSA) position has been established and funded within the GCRC. It is staffed by a bilingual pediatrician/medical ethicist who provides additional attention to the informed consent process and protection of human research participants during the implementation of studies as well as during their review. In addition to other responsibilities, the RSA has the following duties:
  - (a) Review all Pediatric Clinical Research Center (PCRC) protocols prior submission to the IRB and the joint Georgetown University Advisory Committee (GAC):
  
  - (b) Render advice regarding research consent language level and style, and ensure appropriate translations for consents and availability of bilingual staff for obtaining informed consent from research participants;
  
  - (c) Assist investigators in formulating and GAC in reviewing data and safety monitoring plans.
  
  - (d) Observe research consent process periodically - at least once per protocol - and provide feedback to the Principal Investigators and PCRC staff about the appropriateness of the environment, level of language used, and apparent degree of understanding on the part of the research participants. The RSA will ensure that research participants' and their families' questions or concerns are reported to the Principal Investigators and are addressed.

- (e) Provide in English and Spanish (the predominant language of patients seen at CNMC) appropriate educational material for research participants and their families, including, but not limited to:
    - (i) The Clinical Research Process at CNMC.
    - (ii) Issues related to Phase I/II clinical trials and other research that is above minimal risk.
    - (iii) The RSA position, its function, and contact information should research participants have concerns or questions related to the clinical trial performed at CNMC.
  - (f) Prepare, post and annually review the mission statement for RSA activities; and
  - (g) Function as a liaison to the IRB and GAC for the investigators of the PCRC.
5. Progress in the protection of human research participants is on-going, and additional initiatives are in the process of being implemented:
- a. A *Computerized Adverse Event Reporting System* (CAER) has been developed at Georgetown University Medical Center (our satellite GCRC) and is being evaluated for importation to CNMC. The project's objectives are to establish processes for the identification, reporting, and analysis of Serious Adverse Events (SAEs) and the implementation of a system that includes defining SAEs, conducting an analysis when an SAE occurs, and developing strategies to reduce the risk of similar incidents occurring in the future.
  - b. A web-based submission and review system is being prepared in order to reduce the complexities and inaccuracies that can arise with a paper-based system. It is planned to implement one of two systems currently being evaluated next year.
  - c. Certification of the entire IRB staff as *IRB Professionals* is planned for this next year. This will require documentation of extensive experience and completion of appropriate testing.

- d. IRB accreditation is now being offered nationally through two organizations, and the CNMC/CRI IRB will undergo certification once the web-based submission system is in place.

## **II. ENHANCED COMPLIANCE**

### **A. MEDICAL MONITOR**

1. CNMC will select a medical monitor (M/M) for Dr. Batshaw's noninfrastructure clinical research projects with the consent of the United States. The following duties and conditions of the M/M will apply:
  - a. M/M will not be affiliated with CNMC or related institutions or, in the event that Dr. Batshaw leaves CNMC, his current employer.
  - b. M/M will have the expertise to fully understand the subject matter of the clinical trial.
  - c. M/M will meet in person with Dr. Batshaw and gain a thorough understanding of the hypothesis, goals, risks and benefits of the study.
  - d. M/M will report directly to the Audit and Compliance Committee of the IRB, which, in turn, reports to the Consumer Affairs Committee of the CNMC Hospital Board, which, in turn, reports to the full Board of CNMC.
  - e. M/M will review all of Dr. Batshaw's required filings with governmental agencies and with institutional IRBs, as well as the reports of all SAEs.
  - f. M/M will have the unilateral authority to take whatever action s/he deems appropriate, including, but not limited to:
    - (1) Contacting the IRB and reporting a concern.
    - (2) Contacting the CNMC IRB Audit and Compliance Committee and reporting a concern.
    - (3) Contacting the appropriate federal agency and reporting a concern.
    - (4) Contacting the sponsor and reporting a concern.

- (5) Halting the study temporarily.
  - (6) Stopping the study.
- g. If the M/M reports a concern to the IRB that relates to patient safety, the IRB Audit Committee will conduct an investigation and make findings and recommendations to the IRB. A copy of the IRB report will be provided to the M/M. The M/M will report to the appropriate NIH institute and/or FDA the actions taken by the IRB and an assessment of the action taken by the IRB to address the concern.
  - h. The M/M will make semi-annual reports to the NIH institute and/or FDA advising of the status of existing clinical research. The M/M will provide an assessment of current compliance by Dr. Batshaw and Children's Research Institute with regulatory requirements.
  - i. The M/M will be subject to the approval of the FDA or the NIH institute granting the research award.
  - j. Pursuant to the approval of NIH, CNMC has chosen Hugo Wolfgang Moser, M.D. to serve as the M/M.
    - (1) Dr. Moser is currently a faculty member at the Kennedy Krieger Institute in Baltimore, M.D. and holds the rank of the endowed University Professor of Neurology at Johns Hopkins University School of Medicine.
    - (2) Dr. Moser is a pediatric neurologist with a special interest in inborn errors of metabolism (adrenoleukodystrophy). He has extensive experience with NIH and FDA procedures and his work has focused on clinical trials and new drug development.
- 2. Dr. Batshaw will make semi-annual reports to the NIH and/or FDA and to respective IRBs on all of his noninfrastructure clinical research projects.

**B. RESEARCH ADMINISTRATOR/CRO**

- 1. In addition to the M/M, a research administrator (R/A) or a Contract Research Organization (CRO) will be designated to oversee the regulatory compliance of all noninfrastructure clinical research projects for which Dr. Batshaw serves as the Principal Investigator or otherwise participates in a clinical trial. The duties of the R/A or CRO will include, but not be limited to, the following:



- a. Review all submissions and reports to the sponsor, IRB, and government agencies, for compliance with regulations applicable to clinical research and this Agreement and ensure they are submitted in a timely manner. In addition, the R/A or CRO will review all source data generated or utilized by Dr. Batshaw as part of its review. The R/A or CRO will also ensure that the appropriate approved informed consent form is used and that the study is conducted in accordance with the approved protocol.
- b. Review all correspondence to and from off-site locations, other institutions and the NIH and/or FDA relating to all noninfrastructural clinical trials.
- c. R/A or CRO will have the unilateral authority to take whatever action s/he deems appropriate, including, but not limited to, the following:
  - (1) Contacting the IRB and reporting a concern.
  - (2) Contacting the CNMC IRB Audit and Compliance Committee and reporting a concern.
  - (3) Contacting the appropriate governmental agency and reporting a concern.
  - (4) Contacting the sponsor and reporting a concern.
  - (5) Halting the study temporarily.
  - (6) Stopping the study.
- d. The R/A or CRO will make semi-annual reports to the FDA and/or the NIH depending upon the agency funding the research grant or trial regarding Dr. Batshaw's compliance with regulations applicable to clinical research and this Agreement.

## **C. ADMINISTRATION**

1. All costs associated with the M/M and R/A-CRO will be borne by CNMC/CRI or the sponsor and/or grant recipient should Dr. Batshaw leave CNMC/CRI.
2. The NIH Division of Grants Compliance and Oversight and the FDA will have the right to conduct unannounced audits of all noninfrastructure clinical research projects in which Dr. Batshaw is involved.

3. The enhanced compliance measures set forth in Section C will remain in effect for not more than three (3) years from the effective date of this Agreement.
4. The enhanced compliance measures set forth herein relate to clinical research where Dr. Batshaw is involved in the research as determined by the NIH and FDA. In the event that Dr. Batshaw relinquishes his role as an investigator in a noninfrastructure clinical research project, the enhanced compliance measures required by this Agreement will no longer apply. However, such requirements will follow Dr. Batshaw should he become affiliated with another institution and participate in noninfrastructure clinical research projects.
5. The effective date of the enhanced compliance measures will be the date of signature of the last signatory to the Agreement, unless otherwise stated in this Agreement.