PROJECT AGREEMENT #G-1081p

BETWEEN

THE INTERNATIONAL SCIENCE AND TECHNOLOGY CENTER,

THE NATIONAL CENTER FOR DISEASE CONTROL AND MEDICAL STATISTICS OF THE REPUBLIC OF GEORGIA

AND

THE DEPARTMENT OF HEALTH AND HUMAN SERVICES OF THE UNITED STATES OF AMERICA

Development of Surveillance System and Control Strategy for Leishmaniasis in Georgia by means of Epidemiological Investigation and Strengthening of Laboratory Capacities
(BTEP ID #89)

Operative Commencement Date: April 1, 2005

1.2c8

Definitions
"Agreement" means an ISTC project agreement
"Party" means a Party to the Agreement Establishing an International Science and Technology Center
"Financing Party" means a Party providing funds for an ISTC project (The United States Department of Health and Human Services through the BTEP program);
"Partner" means an organization that has been approved by the ISTC Governing Board to participate in the ISTC Partner Program on a regular basis (The U.S. Department of Health and Human Services) and acts as an ISTC partner;
"Recipient" means an organization of the Russian Federation or other country of the former Soviet Union, which conducts work under an ISTC project agreement

The International Science and Technology Center (hereinafter referred to as "**the Center**"), the **National Center for Disease Control and Medical Statistics of the Republic of Georgia** (hereinafter referred to as "**the Recipient**"), and the **U.S. Department of Health and Human Services** (hereinafter referred to as the "**Partner**"), represented for the purpose of the signature of this Project Agreement (hereinafter referred to as "**the Agreement**") by their authorized representatives (with the Center, the Recipient, and the Partner hereinafter referred to collectively as "**the Signatory Parties**"),

TAKING INTO ACCOUNT THE FOLLOWING CONSIDERATIONS:

The United States of America, Japan, the Russian Federation and, acting as one Party, the European Atomic Energy Community and the European Community (with these two organizations hereinafter referred to as "**the European Community**") signed the Agreement Establishing the International Science and Technology Center on November 27, 1992 (hereinafter referred to as "**the ISTC Agreement**") and the Protocol on Provisional Application of the Agreement Establishing the International Science and Technology Center on December 27, 1993 (hereinafter referred to as "**the ISTC Protocol**"),

The Republic of Georgia, the Republic of Armenia, the Republic of Belarus, the Republic of Kazakstan, the Kyrgyz Republic, Norway, the Republic of Korea, the Republic of Tajikistan and Canada have acceded, and additional States may accede, to the ISTC Agreement and to the ISTC Protocol to participate in the activities of the Center,

The Center is a legal entity and has been registered by the Ministry of Foreign Affairs of the Russian Federation as an international organization with its headquarters in Moscow,

The Recipient is a legal entity within the Republic of Georgia,

The Partner, established as a U.S. Federal Department under U.S. law and having its principal office in Washington, DC, is a legal entity that has been approved by the Center's Governing Board to participate in Center activities as an ISTC Partner, in accordance with the Memorandum of Agreement between ISTC and DHHS signed on July 6, 1999 and August 10,1999.

The Governing Board of the Center has approved a project to be funded by the Partner through the Center in the domain covered by the Agreement concerning cooperation in approved projects in the health sector to facilitate the non-proliferation of weapons and weapons expertise.

The Partner has agreed to provide financial support for such project, under the DHHS Biotechnology Engagement Program (BTEP) and in accordance with the Article II, paragraph 2 of the Memorandum of Agreement.

As set forth in the ISTC Agreement, funds received by a legal entity in connection with the Center's projects shall be excluded in determining the profits of that organization for the purpose of tax liability and funds received by persons in connection with the Center's projects shall not be included in these persons' taxable incomes,

All parties to this Project Agreement shall conduct this project of work consistent with the principles of the ISTC Statute provisions and applicable international conventions and agreements for which the USA and Republic of Georgia are Parties.

HAVE AGREED AS FOLLOWS:

Article 1 - Scope of the Agreement

1.1 The Recipient shall carry out the work plan set forth in Annex I according to the conditions of the Agreement, subject to the provisions of the ISTC Agreement, the ISTC Protocol, the Statute of the Center (hereinafter referred to as "**the ISTC Statute**"), and the Principles for Partner Participation in ISTC Activities, which govern in case of conflict. The activities carried out under the Agreement are entitled: **Development of Surveillance System and Control Strategy for Leishmaniasis in Georgia by means of Epidemiological Investigation and Strengthening of Laboratory Capacities** – BTEP Project ID#89; (hereinafter referred to as "**the Project**").

1.2 Subject to any special conditions in Article 11 or any amendments or exclusions by any other Articles, the detailed terms of the Agreement are specified in the Annexes that form an integral part of the Agreement. In the case of conflict between any provision in the Annexes and any other provision of the Agreement, the latter shall prevail.

1.3 The Partner may request through the Center access to the Project site for the consultation on and the evaluation of the progress of the Project. The Recipient shall use its best efforts to comply with such requests.

Article 2 - Duration of the Project

The duration of the Project is estimated to be 36 months from April 1, 2005 (hereinafter referred to as "**the Operative Commencement Date**").

Article 3 - Sub-agreements with Other Participating Institutions

There are no sub-agreements relating to the Agreement.

Article 4 - Financial Contribution of the Partner through the Center

4.1 The total cost of the Project to the Center shall not exceed US$414,274.00 (Four hundred fourteen thousand two hundred seventy four dollars and zero cents). This total includes:

(1) items to be reimbursed in cash to the Recipient in accordance with Article 4.3,
(2) grants in cash to be made by the Center directly to the individual participants in the Project (hereinafter referred to as "**Individual Participants**") for financial support of the Individual Participants in accordance with Article 4.4, and
(3) items to be provided in-kind by the Center to the Recipient in accordance with Article 4.5.

After further consideration of the costs and availability of the items to be provided, the Recipient may, with the concurrence of the Center's representative, interchange items between Articles 4.3 and 4.5 with corresponding adjustments of the cost estimates for each Article.

4.2 The Partner shall provide to the Center project funds consistent with the bilateral financial Memorandum of Agreement between the Center and the Partner no later than the Operative Commencement Date of the Project.

4.3 The Center shall reimburse the Recipient for expenditures by the Recipient in accordance with Annexes I and II. The estimated cost of such expenditures is US$23,770.

4.4 The Center shall make direct grants in dollars to Individual Participants in the Project in accordance with Annex I at an estimated cost of US$254,184. This amount can be increased at the request of the Recipient and with the concurrence of the Center's representative and of the affected Individual Participants provided the costs of Article 4.3 and/or Article 4.5 are reduced accordingly.

4.5 The Center's in-kind contributions to the Recipient are estimated at US$136,320. These in-kind contributions will be provided in accordance with the lists of items to be provided and the timetables set forth in Annex I in order to enable the Recipient to meet the work schedule for the Project. Failure by the Center to provide the in-kind contributions in a timely manner may give rise to a modification of the relevant provisions of the Agreement.

The Center's in-kind contributions, which are provided for exclusive use on the Project by the Recipient during the lifetime of the Project, include the following categories of items:

4.5.1 The Center shall provide in-kind equipment to the Recipient (if any) in accordance with Annex I (hereinafter referred to as "**Center Provided Equipment**"). Center Provided Equipment will be delivered to the Recipient at a CIS customs entry point specified by the Center. The Center will be responsible for clearance through customs, and the Recipient will be responsible for transporting the equipment from the customs entry point to the site of the Project. The equipment shall be inventoried, preserved, accounted for, and maintained throughout the Project by the Recipient. The equipment shall be used only in areas that are open for monitoring and auditing in accordance with Article 9. The title to Center Provided Equipment with an acquisition per item cost of less that $2,500 will vest in the Recipient once it has been provided. The title to all other Partner Provided Equipment will remain with the Center, unless mutually agreed otherwise.

4.5.2 The Center shall provide in-kind materials in accordance with Annex I (hereinafter referred to as "**Center Provided Materials**"). Center Provided Materials will be delivered to the Recipient at a CIS customs entry point specified by the Center. The Center will be responsible for customs clearance, and the Recipient will be responsible for transporting the materials to the site of the Project.

4.5.3 The Center shall provide in-kind services (if any) in accordance with Annex I (hereinafter referred to as "**Center Provided Services**").

4.5.4 The Center shall provide in-kind international travel by the Recipient in accordance with Annex I (hereinafter referred to as "**Center Provided Travel**"). The cost of the Center's contribution will not exceed US$29,050.

Center Provided Travel will be undertaken by participants in the Project only after advance approval for each trip by the Partner and notification to the Center. The Recipient shall send to the Partner and Center requests for travel not less than 30 days prior to the beginning of each trip unless a shorter time for advance request is approved by the Partner and then by the Center for a specific trip. The Center will provide directly to the traveler the funds to cover such travel, provided that such travel is approved by the Partner prior to the beginning of the travel.

The Center's responsibility does not include making arrangements for visits, passports, visas, or travel reservations but is limited to providing financial support, including funds to cover the costs of passport and visa fees as well as transportation and lodging, in accordance with the travel regulations of the Center.

The Recipient is responsible for ensuring that the financial support requested pursuant to this paragraph does not exceed the financial limit set forth above.

4.5.5 The Center shall provide in-kind the costs of certain bank transfer fees in accordance with Annex I (hereinafter referred to as "**Center Provided Bank Fees**"). They will be limited to fees necessary to transfer funds into the bank account or accounts of the Recipient and fees associated with the payment of cash to Individual Participants in the Project. They will be paid directly by the Center to the appropriate banks.

Article 5 - Cash Payments by the Center to the Recipient

5.1 Pursuant to Article 4.2, the Center shall make its payments to the Recipient through Dedicated Bank Account(s), as set forth in Article 6. 6 of Annex II in banks acceptable to the Center.

- An advance payment of US$5,527 which is the estimated level of expenditures by the Recipient during the first six months of the Project, as soon as possible following the Operative Commencement Date;
- Quarterly payments within one month of the receipt by the Partner and Center of progress or annual reports and associated cost statements in accordance with Article 7 and Annexes II and III. The amounts of the payments shall be estimates by the Center of the funds required to support the work plan set forth in Annex I during each of the succeeding quarters taking into account the cost statement from the previous period;
- A retention shall be made by the Center of US$11,787. The retention shall be released to the Recipient within one month following the approval by the Partner and Center of the last technical or financial document or other deliverable required by the Agreement.

5.2 Pursuant to Article 4.4, the Center shall make grant payments directly to Individual Participants in accordance with letters of agreement between the Center and the Individual Participants. The Center shall ensure that banking arrangements are established for these payments.

At the end of the third month following the Operative Commencement Date and every three months thereafter throughout the duration of the Project, the Recipient represented by the Project Manager who is identified in Annex I will provide the Partner and the Center with a list of grant payments that are due at that time to Individual Participants in accordance with the payment levels set forth in Annex I and the amount of time devoted to the Project by each Individual Participant as certified by the Project Manager. Such payments will then be promptly made as appropriate by the Center.

Since the Individual Participants will remain employees of the Recipient, the Center's act of direct grant payments to the Individual Participants will not transfer from the Recipient to the Partner or the Center any liability for damages caused by the Individual Participants during execution of the Projects or any liability for damages to the Individual Participants during execution of the Project.

Article 6 - Cost Statements by the Recipient

6.1 Quarterly cost statements shall be submitted by the Recipient to the Partner and the Center as follows:

To the Center, the Partner and the U.S. Counterpart Scientist:
– English: one copy via electronic transmission (e-mail or on diskette) and one printed copy;

The first statement is to be submitted no later than four months after the Operative Commencement Date and will cover the first three months of Project activity. Subsequent statements are to be submitted at three-month intervals following submission of the first statement. The statements will be appended to the relevant technical reports specified in Article 7. The cost statements will include the costs of grant payments directly to Individual Participants, but the requests for such grant payments in accordance with Article 5 should not be delayed pending preparation of the entire quarterly cost statements called for in this Article. Such payments may be nevertheless suspended by the Center in case if the cost statement for the previous quarter was not yet submitted to the Center.

6.2 A consolidated cost statement shall be submitted by the Recipient to the Partner and the Center within two months of the completion, cessation or termination of the work financed by the Partner as follows:

To the Center, the Partner and the U.S. Counterpart Scientist:
– English: one copy via electronic transmission (e-mail or on diskette) and one printed copy;

If such a statement is not submitted on time, the Center or the Partner may request in writing its submission. If the Center and the Partner do not receive the submission within thirty days after such a written request, the Center, in consultation with the Partner, may consider the previously claimed costs to be final and determine to make no further reimbursement.

6.3 Cost statements shall comply with the formats prescribed in Annex III.

Article 7 - Reports and Other Project Outputs

7.1 The Recipient shall submit the following reports in accordance with the format prescribed in Annex III as follows:

To the Center, the Partner and the U.S. Counterpart Scientist:
– English: one copy via electronic transmission (e-mail or on diskette) and one printed copy;

It is the responsibility of the Recipient, in consultation with the Partner, to indicate clearly what parts of reports and other project outputs contain invention or business confidential information and specify any limitations on circulation. For each report or other project output, an unrestricted version shall also be provided. All reports containing invention or business confidential information shall be handled by the Center according to established internal procedures.

- Quarterly progress reports covering each three-month period following the Operative Commencement Date to be submitted within fifteen days after the end of each reporting period.

- Annual reports. For projects of duration of more than one year, an annual report will be submitted 13 months after the Operative Commencement Date and will cover the first year of project activity. For projects of duration of more than two years, a second annual report will be submitted 12 months later.

- Other reports. The Recipient and the Partner will define other reports in Annex I.

- A final report. A draft final report will be submitted to the Center and the Partner within two months of the completion of the Project work plan, cessation or termination of the Agreement, or the agreed completion date of the Agreement, whichever is the earliest. The Partner, in consultation with the Center, shall submit to the Center and Recipient its evaluation and comments on the draft final report within two months after receipt of the latter. The definitive final report will then be submitted by the Recipient to the Center and the Partner within one month after receipt of the Partner's evaluation. If the Partner does not submit an evaluation within two month, the draft final report shall be considered the definitive final report.

- Edited reports for publication will be provided as specified in Article 4.1 (c) of ANNEX II.

7.2 For the purposes of the Agreement, "deliverables" are defined as any significant outputs, including all reports, of the Project to be submitted in accordance with Annexes I, II and III.

Article 8 - Ownership and Exploitation of Results

8.1 The results arising from the Agreement shall be allocated between the Recipient and the Partner in accordance with Part E of Annex II. The Recipient and the Partner shall take appropriate action to exploit or commercialize the results and to make available the results to third parties in accordance with the framework specified in Part E of Annex II. Cooperation agreements with foreign institutions complementing, but not conflicting with, this Framework may be entered into by the Recipient and the Partner.

8.2 Prior to completion of the Project, the Recipient shall submit to the Center a Technology Implementation Plan developed in consultation with the Partner. For projects with a duration of eighteen months or longer, this Plan will be submitted 6 months prior to the anticipated Project completion date. For projects with a duration of less than eighteen months, the Plan will be submitted three months prior to the anticipated Project completion date.

8.3 Exploitation of results shall be limited to applications for peaceful purposes. In this regard, the Recipient and the Partner shall ensure that any results which could result in concerns over proliferation of weapons technology and transfer of sensitive technologies will be protected in accordance with relevant laws of the Republic of Georgia and international agreements and conventions to which the Republic of Georgia is a Party.

Article 9 - Auditing and Monitoring

9.1 Access by the Center to carry out on-site monitoring of all technical activities of the Project shall be granted by the Recipient, and information and assistance shall be given for the verification and evaluation of the Project activities as set out in Annex II.

9.2 Financial audits of costs may be carried out by the Center as specified in Annex II.

9.3 Auditing and Monitoring of institutions located in closed cities shall be carried out according to the procedures adopted at the sixth Governing Board Meeting of the Center.

Article 10 - Amendments, Variations, or Additions

The provisions of this Agreement and its Annexes may be amended or supplemented only by means of a written agreement signed by authorized representatives of the Signatory Parties. However, operational changes in Annex I, other than changes in the Project Manager, the Participating Institution, daily rates of leading persons of the Project and the overall schedule, can be made by agreement between the Center and the Recipient.

Article 11 - Special Conditions

11.1 With respect to the Protection of Human Subjects

(i) NIH/NIAID has reviewed the proposed activities and found that they do consist of research involving human subjects.

(ii) The project proposal must be reviewed in accordance with the U.S. law and international policies and regulations regarding biomedical research involving human subjects

(iii) The Implementing Agencies shall be responsible for ensuring that any research work conducted under this project Agreement shall be carried out consistent with The Public Health Service Act as Amended by the Health Research Extension Act of 1985 and the Federal Policy for the Protection of Human Subjects of 1991

(iv) The Recipient and the Partner shall follow the principles of *The Belmont Report, Principles and Guidelines for Protection of Human Subjects of Research* or *The World Medical Association Declaration of Helsinki, Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects*, adopted by the 18th World Medical Assembly and revised in 1989.

11.2 With respect to the use of Laboratory Animals

(i) Laboratory animals and/or endangered species are not expected to be a subject of this research or be involved during the execution of work under this specific project.

(ii) However, if this proves otherwise, the project proposal must be reviewed in accordance with the U.S. law and international policies and regulations regarding biomedical research involving laboratory animals

(iii) The Implementing Agencies shall be responsible for ensuring that any activity carried out pursuant to this agreement and involving laboratory animals is in compliance with the Foreign State of Compliance, International Guiding Principles for Biomedical Research and the Public Health Service Policy on Humane Care and Use of Laboratory Animals as revised in September of 1986

11.3 With respect to transport of Biological Samples

Any export/import involving transportation of biological samples shall be conducted in accordance with the existing laws, regulations, and administrative procedures of the United States of America and the Republic of Georgia. For current information regarding this issue please contact the following:
(i) For U.S. exports: Department of Commerce, Bureau of Export Administration at (202) 482-4811.

(ii) For U.S. imports of etiologic agents of humans: Centers for Disease Control and Prevention, Office of Health and Safety at (404) 639-2453.

(iii) For U.S. imports of etiologic agents of livestock, poultry and other animals: United States Department of Agriculture, Animal and Plant Health Inspection Service, Veterinary Services at (301) 734-3277.

11.4 With respect to Manipulation of Genetic Material through the Use of Recombinant DNA Techniques

(i) NIH/NIAID has reviewed the proposed activities and found that they do not consist of research involving recombinant DNA techniques for genetic manipulation.

(ii) However, if this proves otherwise, the project proposal must be reviewed in accordance with applicable U.S. law and international policies and regulations, including the current "NIH Guidelines for Research Involving Recombinant DNA Molecules." These guidelines can be found on the NIH website at http://www.nih.gov/od/oba or from the NIH Office of Recombinant DNA Activities (301-496-9838).

(iii) The BTEP Advisory Group may ask the investigators to initiate a review by the appropriate Recombinant DNA Advisory Committee (RAC) or Institutional Biosafety Committee (IBC) at any time.

Article 12 - Disputes

Disputes arising during performance of this Agreement including, in particular:
(i) A claim by the Recipient for any payments deemed due;
(ii) An interpretation of a provision of the Agreement; or
(iii) A request for relief or approval related to the Agreement,

shall be subject to the following procedure:

The Recipient shall submit any claim, demand, or request in writing to the Partner and to the Center. The Partner and the Center will prepare a joint response. Unless a longer period is specified in the Agreement, the written decision of the Partner and the Center shall be delivered to the Recipient within four weeks of the receipt of the submission.

Exceptionally, the Recipient may appeal the Partner's and Center's decision in writing through the Executive Director of the Center to the Governing Board of the Center within four weeks of the communication of the Partner's and Center's decision.

The decision of the Governing Board shall be final and binding (unless otherwise provided). Pending the final settlement of disputes, the Recipient shall, nevertheless, proceed diligently with the performance of the Agreement.

Article 13 - Liability

13.1 The Partner and the Center shall not be liable for any material loss, damage, or injury of any nature arising from, or in connection with, the performance of the work under the Agreement solely by virtue of

financing the Project, including liability from direct grant payments to Individual Participants as set forth in Article 5.2.

13.2 The Partner and the Center shall not be liable to the Recipient or third parties for claims arising from:

- publication or transmission of any report in accordance with Articles 4 and 13 of Annex II unless it is shown that the Partner or Center have not taken reasonable steps to protect material clearly indicated as invention or business confidential information;
- the application of the contents of any report by a third party; or
- the handling or use of products which result from the Project.

13.3 The Center shall not be liable for nonperformance by the Partner or the Recipient of their obligations under the Agreement.

Article 14 - Suspension and Termination of the Agreement

14.1 Suspension

14.1.1 If the Center identifies a problem with the Project's performance through audit, monitoring, annual reports or other ways, and discussions between the Center and the Recipient which shall ensue pursuant to a notice given by the Center to the Recipient do not produce any results, the Center shall reserve the right to suspend, in consultation with the Partner, the project or, when feasible from technical and other points of view, a part of the Project, within thirty days after the Center issues to the Project Manager a notification of suspension which specifies the problem, the effective date and the period of the suspension. In case auditing and monitoring procedures stipulated in the Agreement and Annex II are breached by the Recipient, the suspension shall come into force ten days after the notification given to the Recipient if no corrective action has been taken during this period.

When the suspension becomes effective, the Center shall pay grants to the individual participants for the period they were engaged in the Project before the Center's declaration of suspension becomes effective. Any other payments or in-kind supplies to the Recipient shall in principle be suspended as long as the suspension remains in effect. The Recipient shall act in due diligence to mitigate any losses which may arise during this period.

Even when the suspension is in effect, the Center and the Recipient shall do the utmost to find a possible solution to the problem.

14.1.2 In case the Center and/or the Partner does not fulfill its obligations arising from the Project, namely in relation to Article 2 and 3, the Recipient shall reserve the right to suspend the Project within thirty days after the Recipient issues to the Executive Director of the Center a notification of suspension which specifies the problem, the effective date and the period of the suspension. Clauses of paragraph three of 14.1.1 shall be applied here as well.

14.2 Termination

14.2.1 When the Project is suspended by the Center, and the period of the suspension which is specified in the Center's notification expires and the Center and the Recipient are unable to find a solution, the Center shall, in consultation with the Partner, terminate the Project. In the event of partial suspension, the Center and the Recipient shall negotiate and agree upon possible measures including partial termination of the Project. If these negotiations do not produce any viable alternative plan, the Center shall reserve the right to terminate the entire Project.

Notwithstanding the termination, the Recipient shall submit reports and cost statements covering the period up to the termination and the following provisions of the Agreement shall continue to apply: Article 12 (Disputes), Paragraph 7 (Accounting Principles, Allowable Costs, and Transfer of Costs) and 8.2 (Equipment) of Annex I of the Agreement, and Part E of Annex II of the Agreement (Information and Intellectual Property).

If the Project is terminated, costs shall be limited to the allowable costs incurred by the Recipient prior to the suspension and other costs which the Center considers to be fair and reasonable having regard to commitments which have been reasonably entered into and which cannot be canceled or avoided.

14.2.2 When the Project is suspended by the Recipient, and the period of the suspension which is

specified in the Recipient's notification expires and the Recipient and the Center are unable to find a solution, the Recipient shall terminate the Project. Clauses of paragraphs two and three of 14.2.1 shall be applied here as well.

14.3 Termination by Force Majeure Situations

When Force Majeure situations occur which make the Project implementation impossible, the Center in consultation with the Partner and the Recipient may terminate the Project with application of similar procedures as specified above.

14.4 Termination Forced due to the Violation of Laws or Regulations by the Recipient

When the Recipient has committed actions which obviously violate the national laws of the state where the Recipient is a legal entity or which obviously are contrary to the stated objectives of the Center or to other conditions specified under the ISTC Agreement or the ISTC Statute, the Center shall terminate the Project with immediate effectiveness upon written notification of termination to the Recipient. In this case, the Recipient shall promptly return to the Center all payments and goods previously provided to the Recipient. Notwithstanding any termination, Part E of Annex II of the Agreement will continue to apply.

Article 15 - Correspondence

15.1 Any written notice, request or consent required under the Agreement is deemed to have been given or made when delivered in person to an authorized representative of a Signatory Party or when sent by mail, telex, telegram, electronic mail or facsimile (receipt acknowledgment required) to such Signature Party at the following address:

For the Center:
International Science and Technology Center
Ulitsa Luganskaya 9,
Moscow 115541, Russia
Facsimile 7/095-797-6047
Senior Project Manager: Marina Amzashvili

For the Institute:
National Center for Diseases Control
9 Asatiani Str, Tbilisi 380060 Georgia
Facsimile: (995 32) 43 30 59
Project Manager: Eka Giorgobiani

For the Partner
Office of Global Health Affairs
U.S. Department of Health and Human Services
5600 Fishers Lane, Room 18-90
Rockville, MD 20857
Facsimile: 301-443-0742
Executive Secretary: Susanna K. Partridge

For the U.S. Counterpart Scientist:
Laboratory of Parasitic Diseases, NIAID, NIH
4 Center Drive, MSC 0425
Bethesda, MD, 20892, USA
Facsimile: (301) 480-3708
US Counterpart Scientist: David L. Sacks

15.2 Notice will be deemed to be effective as follows:

(i) in the case of personal delivery or mail, on delivery;

(ii) in the case of telexes, telegrams, electronic mail or facsimiles, within one (1) working day following confirmed transmission. A signed original will be provided by mail in all cases.

15.3 Each Signatory Party may change its address for notice hereunder by giving the other Party notice of such change pursuant to this Article.

Article 16 - Annexes

As specified in Article 1.2, the Annexes are an integral part of the Agreement. They are:

Annex I	Work Plan
Annex II	General Conditions
Annex III	Formats for Progress and Cost Reports
Annex IV	Disclaimer

Article 17 - Entry into Force of the Agreement

The Agreement shall enter into force on April 1, 2005.

Prepared in Moscow in the English language.

For the Center:

25-5-05
Date

Norbert Jousten
Executive Director
International Science and Technology Center

For the Recipient:

31.05.05
Date

Paata Imnadze
Director
National Center for Disease Control and Medical Statistics

For the Partner:

24 May 2005
Date

Susanna K. Partridge
Executive Secretary
DHHS Biotechnology Engagement Program (BTEP)

ANNEX I
Work Plan
I. Summary Project Information

1. Project Title

Development of Surveillance System and Control Strategy for Leishmaniasis in Georgia by means of Epidemiological Investigation and Strengthening of Laboratory Capacities.

2. Project Manager

Name: Eka Giorgobiani	
Title: Candidate of Biological Sciences (PhD)	**Position:** Head of Information Resources Department
Street address: 9, Asatiani str.	
City: Tbilisi	**Region:**
ZIP: 0177	**Country:** Georgia
Tel.: (995 32) 31 14 66	**Fax:** (995 32) 43 30 59
E-mail: egiorgobiani@yahoo.com	

3. Participating Institutions

3.1. Leading Institution

Short reference: NCDC	
Full name: National Institute for Disease Control and Medical Statistics.	
Street address: 9, Asatiani str.	
City: Tbilisi	**Region:**
ZIP: 0177	**Country:** Georgia
Name of Signature Authority:	**Paata Imnadze**
Title: Candidate of Medical Sciences	**Position:** Director
Tel.: (995 32) 39 89 46	**Fax:** (995 32) 43 30 59
E-mail: pimnadze@ncdc.ge	
Governmental Agency: Ministry of Labor, Health and Social Affairs.	

3.2. Other Participating Institutions

None

4. Foreign Collaborators/Partners

4.1. Collaborators

Institution: Laboratory of Parasitic Diseases, NIAID, NIH.	
Street address: 4 Center Drive, MSC 0425	
City: Bethesda	**Region/State:** MD
ZIP: 20892	**Country:** USA
Person: David L. Sacks	
Title: PhD	**Position:** Head, Intracellular Parasite Biology Section
Tel.: (301) 496-0577	**Fax:** (301) 480-3708
E-mail: dsacks@nih.gov	

4.2. Partners

Institution: DHHS Biotechnology Engagement Program (BTEP).	
Street address:	**5600 Fishers Lane, Parklawn Bldg.**
City: Rockville	**Region/State: MD**
ZIP: 20857	**Country: USA**
Signature Authority:	**Susanna Partridge**
Title: MPH	**Position: BTEP Executive Secretary**
Tel.: +1 301 443 0585	**Fax: +1 301 443 0742**
E-mail: spartridge@osophs.dhhs.gov	
Project Coordinator:	**Yelena Shnayder**
Title: MS	**Position: International Health Officer**
Tel.: +1 301 443 0623	**Fax: +1 301 443 0742**
E-mail: yshnayder@osophs.dhhs.gov	

5. Project Duration

36 months

6. Project Location and Equipment

Institution	Location, Facilities and Equipment
Leading Institution	The NCDC is primary public health center in Georgia with several diagnostic and research laboratories and staff of 217 workers, including microbiologists, epidemiologists, researchers, veterinarians, and public health service administrators. The NCDC headquarters are located in downtown Tbilisi and occupy more than 6 500 sq m in four buildings. Study will be carried out: at NCDC – in 4 rooms of laboratory N2207 on the second floor of the building II, with total area about 80 sq m, and 5 work rooms – N1203 (3 rooms) on the second floor of the building I and N3104 (2 rooms) on the first floor of the building III; at the Institute of Medical Parasitology and Tropical Medicine – in 6 rooms NN102, 103, 104, 305, 306, 307. The following equipment is available in laboratories for experimental and research activities of the project: Thermocyclers: Flexigene (Techne, UK), Genius (Techne, UK). VerTech (Techne, UK). Genofuge 16M (Techne, UK). Genesys 10uv (Thermo Spectronic). Shaking Bath SB-16 (Techne, UK). BioMax QS710 (Kodak) – electrophoresis. Electronic U.V. Transilluminator (Ultra Lum). Standard Heatblock (VWR Scientific). PFGE apparatus CHEF-DRII (Bio-Rad). Luminous microscope, light microscopes, centrifuge, thermostats, freezer, autoclave, desiccator, PH meter.
Participant Institution 1	None

II. Specific information

1. Introduction and Overview

In the past several years a critical situation has developed in Georgia concerning visceral leishmaniasis (VL). Since 1990, the number of cases recorded annually has increased 10 fold, with the majority of these occurring within new, emerging foci in the capital of Georgia - Tbilisi.

In total, 1944 cases of VL were registered in the country from 1928 to August, 2004. 47% of these cases have been registered in the past decade, during which time the number of cases has increased 10-fold, from 12 cases in 1991 to 125 cases in 2001. Special attention has to be paid to the critical situation in Tbilisi, where beginning from 1990 new active foci of the disease have emerged; 72 of the 101 cases detected in 2002, 70 of 104 – in 2003 and 62 of 93 – in 2004 from January to September, are from Tbilisi. In general, the active foci of VL in Tbilisi are districts located in woody piedmont areas, although sporadic cases are registered in other districts as well *[7]*. About 58.3% of the patients in Tbilisi are 1-4 years old, while 17.4% are 0-1 yrs, and 15.6% are 5-14 yrs. It is important to point to the increase of VL cases among adults during the last several years; they consist of 8.7% of the total number of cases registered in 1990-2002 (65 from 745 cases).

Due to the poor economic conditions following the civil war in 1990, it became difficult to implement control measures, or to insure proper diagnosis and timely treatment of patients with VL. Of the 411 patients registered in 1986-1998, their diagnosis of VL after manifestation of clinical signs took 20 days for 53 patients, 1 month – 127 patients, 2 months – 57, 3 months – 47, 4 months – 37, 5 months – 27, 6 months – 27, 7 month – 17, 8 months – 5, 9 months – 4, 10 months – 1, 11 months – 1, 2 years – 2, and 3 years – 1 *[7]*. Delayed or misdiagnosis of VL is due to the failure to use the modern, accurate diagnostic tests that are available, the absence of trained medical personnel (especially in rural areas), and the absence of information in the population about the disease. In accordance with data from the Research Institute of Medical Parasitology and Tropical Medicine (RIMPTM), collected from different medical organizations in Georgia, because of incorrect diagnoses serious medical errors have occurred, such as laparotomy or splenectomy, which in many cases were fatal. Twelve lethal cases of VL have been recorded in Georgia since 1995. The cause for death in all these cases was incorrect or late diagnosis *[6]*. Another probable consequence of late diagnosis and treatment is the significant rise of relapse cases; 38 patients of 708 registered from 1996 had relapses that occurred within 3-4 months after treatment. Furthermore, 18 antimony unresponsive cases (17 children and 1 adult) were revealed in 1996-1999; these patients required 2 and more additional cycles of treatment with the same or alternative antileishmanial drugs, either glucantime, pentostam, or pentamidine *[7]*.

The last time a systematic study of infection reservoirs in Georgia was carried out during 1960-1970, when researchers from RIMPTM conducted surveys of wild and domestic animals in active and extinct foci of disease. Investigations were carried out using aspirates from parenchymal organs and bone marrow to detect amastigotes. Infected dogs as well as foxes, jackals, and badgers were found in 18 (50.4%) of 35 micro-foci of VL.

With respect to sandfly vectors of Leishmaniasis in Georgia, it again needs to be emphasized that no investigations have been undertaken in the last 14 years. Before that time, entomologists at RIMPTM determined that the dominant phlebotomine species in the eastern endemic areas are *P. kandelakii, P. balcanicus,* and *P. sergenti,* with quantitative prevalence of *P. kandelkii.* No information exists regarding the sandflies involved in the transmission of disease in Tbilisi.

While there is a strong presumption that the *Leishmania* species responsible for all cases of VL in Georgia is *L. infantum,* and that the main infection reservoirs are domestic and stray dogs, these basic epidemiologic aspects have yet to be determined with certainty.

Thus, taking into account the situation described above, there is strong evidence that leishmaniasis surveillance in the country needs to be improved. Surveillance implies unceasing collection, analysis, interpretation and distribution of data. Establishing a surveillance system consists of cycles that begin when cases occur and is completed when information about these cases is made available and is used for prevention and control *[31]*. Random reports only cannot give a true picture. To properly assess the scale of the problem and develop surveillance system, there is an urgent need for more accurate information based on specific studies. Due to the difficult social-economic conditions in Georgia during the last 14 years, it became impossible to study current situation on leishmaniasis outbreak in Tbilisi. No data exists concerning the borders of active foci, the epidemiological significance of the main vector, the role of primary and secondary reservoirs, or the immunological status of the population. Furthermore, identification of the *Leishmania* parasites responsible for

VL and circulating in the different foci, using modern methods for speciation and zymodeme identification, has never been carried out.

The main objective of our proposal is investigation of new active foci of VL, emerged during the last several years in the capital of Georgia – Tbilisi. Study will be carried out with the purpose to obtain data on epidemiological situation in above mentioned foci. Data will be analyzed and these evidence based results then can be generalized and used to make contribution in determination of further actions for development of surveillance system and effective control measures for prevention of VL in all territories of Georgia.

Diagnosis of leishmaniasis in humans and reservoir is crucial for controlling the disease and understanding its epidemiology *[30]*. In its "Program for the surveillance and control of leishmaniasis" *[38]*, World Health Organization gives priorities to early detection, early treatment and notification of leishmaniasis cases; to control of vectors and animal reservoirs; to provide health education and produce training materials. In determination of main tasks for our study we tried to follow these priorities.

Study will include the following tasks:

- Investigation of population living in new active foci, namely, investigation of risk-group consists of children 1-14 years old (we excluded 0-1 age group due to the difficulties related to their examination). Study of population will be performed using epidemiological approaches such as cross-sectional or prevalence study to determine prevalence rate of disease and cohort study in order to identify incidence rate and risk factors for the current outbreak. Based on obtained data we will be able to assess the health status of population in foci concerning leishmaniasis and determine the factors responsible for producing it.
- Investigation of reservoir (stray and pet dogs) of infection. Due to the extensive migration of stray dogs through the city and their location mainly in suburbs, investigation of stray animals will be carried out in whole territory of Tbilisi and its suburbs, whereas pets will be studied only in above mentioned foci. Study will reveal disease prevalence in canine population and confirm animals' reservoir of infection.
- Investigation of the vector of infection will be conducted with the purpose to identify species, determine *Phlebotomus* population density, seasonal and annual density variations, breeding and feeding habits, period of infectivity, factors determining contacts with man. These data will help to determine epidemiological significance of the vector.
- Implementation of modern immunodiagnostic techniques (LST, rK39 ELISA) for serological investigations and the newest molecular-biological methods (RAPD-PCR, RFLP-PCR, ITS-SSCP) for investigation of isolated strains and determination of phylogenetic relatedness between human and canine *Leishmania*.

As a result we will establish in Georgia simple new diagnostic techniques for the early detection and, consequently, rapid treatment of the disease. With the use of new tests for serological diagnosis we will be able to confirm cases, to detect relapses, to reveal subclinical cases, to assess apparent and subclinical case rate, to determine immune status of population at risk. Early and correct diagnosis and identification of *Leishmania* isolates will help to determine the clinical prognosis and to choose an appropriate species-specific therapeutic regimen that will contribute to prevention of relapses. Besides, the application of molecular biology will enable understanding the different links in the transmission cycle of the infectious agent. Implementation of such technology will validate new laboratory tools for diagnosis and investigation of leishmaniasis that strengthen laboratory capacity in Georgia as an important part of surveillance system.

The data obtained after investigation of new emerging foci using above mentioned epidemiological and laboratory approaches will play essential role in further elaboration of appropriate control measures for disease prevention. Once tested and approved in studied foci these control measures can be used as an appropriate strategy for leishmaniasis prevention in whole territory of Georgia or serve as an indicator for changes in epidemiological profile of disease.

During the project we will produce educational materials and conduct trainings for the health personnel and scientists. In total 15 parasitologists and 10 entomologists will participate in proposed actions where will be used materials included new modern methods and approaches applied all over the world, what will rise awareness and advance knowledge of the health workers and promote their professional level.

Activities described in the project will be conducted by scientists previously engaged in research associated with biological warfare who work at the National Center for Disease Control (NCDC), which has the main responsibility for surveillance and control of infectious diseases in all territories of Georgia.

The NCDC is primary public health center in Georgia with several diagnostic and research laboratories and staff of 217 workers, including microbiologists, epidemiologists, researchers, veterinarians, and public health

service administrators. About half of the staff is specialists with university education, and 28 of them have scientific degree (candidates and doctors of sciences).
The NCDC was founded in 1996 on the basis of Georgian Station for Plague Control that was supervised by the Ministry of Health in former USSR. The main office of NCDC is located in Tbilisi, besides, it has branch in Batumi.

The main activities of the Center are:

- surveillance through whole territory of Georgia;
- development and implementation measures against epidemics;
- carrying out epidemiological, diagnostic, bacteriological, virological and molecular-biological investigations;
- coordination of the immunization program;
- development of methodic and normative documents on surveillance, control and prevention of diseases;
- collection and exchange information about infectious and non-infectious diseases inside and outside country; preparation and printing methodic and information materials; providing information to governmental and international organizations.

7 laboratories function at NCDC: Respiratory Diseases; Zoonoses and Anaerobic Diseases; Cholera and Diarrhoeal Diseases; Plague and other diseases with natural foci; Poliomyelitis and other Enteroviruses; Viral and Rickettsial Diseases; Molecular Epidemiology. In these laboratories is carried out isolation and identification of causative agents of these diseases; in addition typing of isolated strains and diagnostics is carried out in molecular-biology laboratory. All isolated strains are catalogued and stored in the NCDC culture collection. The NCDC has the most comprehensive bacterial culture collection in Georgia, with some isolates more than 25 years old.
The NCDC has a broad experience in field surveys, among them:

UNICEF – "Multiple Cluster Survey";

USAID, "Save the Children" – "Drought Nutrition Survey";

US CDC – "Amebiasis outbreak in Tbilisi".

US CDC – "Reproductive Health Survey".

NCDC received grants from several organizations:

WHO - Diphtheria Control, Poliomyelitis Eradication, Malaria Control, Surveillance;

USAID, UNICEF - Immunization, Health Information systems;

USAID, American International Health Alliance - Infection Control, Health Promotion;

Fogarty Foundation – "Emerging Infectious Diseases".

5 projects granted by DHHS-BTEP/ISTC in 2001- Amebiasis, Antibiotic resistance, Tuberculosis, Botulism, Hepatitis C, are extended after successful completion of proposed activities for a periods from 2 quarters to 2 years.

In investigation will be involved medical personnel from Tbilisi Research Institute of Medical Parasitology and Tropical Medicine who have (RIPMTM) a long and broad based experience in diagnosis and treatment of VL. RIMPTM was established in 1924. The main purpose of the Institute is comprehensive study of parasitic and tropical diseases as well as diagnostics and treatment of patients with these diseases.
Hospital on 50 beds, and 2 laboratories, clinical-diagnostic and microbiological, function for today in the Institute. Medical personnel consist of clinicians, laboratory workers, entomologists, and zoologists who have profound knowledge and a long experience in investigation, diagnostics and treatment of parasitic and tropical diseases.
Efficient methods for diagnostics, treatment and prevention of parasitic and tropical diseases have been worked out and implemented during the years of activity. The Institute has a broad experience in conducting of trainings and re-trainings for health personnel from all regions of Georgia who works in this area of medicine; the part of these activities was carried out under the auspice of the World Health Organization.

Clinicians, entomologists, zoologists/veterinarians and laboratory workers from RIMPTM will take part in the project. Clinicians will provide consultations for patients and their examination, collect blood and bone marrow (when necessary) samples, participate in preparation of questionnaires and educational materials, take part in conducting of trainings. Entomologist will participate in collection, preparation, differentiation and identification of *Phlebotomus* species. Zoologists/veterinarians will work with dogs, collect samples and conduct serosurvey. Laboratory personnel will help in cultivation of *Leishmania* isolates.
Laboratory of Parasitic Diseases of the National Institute of Allergic and Infectious Diseases (NIAID, NIH) will be involved in the project as a collaborator. Head and two members of Intracellular Parasite Biology Section of the Institute will participate in all scientific and administrative aspects of the proposal. All three persons were in Georgia in February 2003 and jointly with the Georgian colleagues made preliminary evaluation of current situation in Tbilisi concerning leishmaniasis with the purpose to outline main tasks and activities of the proposal.

2. Expected Results and Their Application

As a result of the basic and applied research activities proposed, we can expect to achieve the following:
- Development and consolidation of a strong system for notification and registration that will give an accurate picture of VL prevalence in Georgia.
- Improvement of surveillance system for VL, including monitoring of infection rates in children and suspected canine reservoirs, and identifying sand fly vectors of disease that will contribute to development of effective measures for control of disease.
- Implementation of modern methods for identification and investigation of *Leishmania* species prevalent in Georgia.
- Development of molecular biology of leishmaniasis in Georgia; introduction of modern molecular biology methods, such as PCR technique, for investigation of leishmaniasis in laboratories of Georgia.
- Improvement of diagnostic methods for VL in Georgia that will make possible early diagnosis and treatment of patients with VL.
- Education and training of health personnel according to up-to-date methods and standards that advance qualifications of Georgian physicians.
- Broadening capabilities for further collaboration between Georgian and US scientists.
- Data obtained in the course of the project will be presented at meetings and conferences as well as published in different scientific journals at the local and international level.

3. Meeting ISTC Goals and Objectives

Proposed project will give opportunities for scientists from Georgia, previously engaged in research associated with biological warfare, to redirect their scientific work toward peaceful activities. As a result of this project they will gain new knowledge and skills and will have favorable conditions to work with modern methods and techniques, that, in turn, will promote development and improvement of basic and applied research in Georgia, advance the professional level of Georgian scientists, and contribute to their integration into the international scientific community.

4. Scope of Activities

The main objective of our proposal is investigation of new active foci of VL, emerged during the last several years in the capital of Georgia – Tbilisi. Study will be carried out with the purpose to obtain data on epidemiological situation in above mentioned foci. Data will be analyzed and these evidence based results then can be generalized and used to make contribution in determination of further actions for development of surveillance system and effective control measures for prevention of VL in all territories of Georgia. Improvement of laboratory methods for diagnosis of VL will make possible earlier diagnosis and treatment, and the application of modern molecular biology methods will make possible the identification and investigation of *Leishmania* species prevalent in Georgia.

Task 1

Task description and main milestones	Participating Institutions
1. Survey of new active foci of VL in Tbilisi. 1.1. Investigation of population. 1.1.1. Development of questionnaire for population.	1 - National Center for Disease Control.

1.1.2. Preparation and distribution of information materials for population. 1.1.3. Cross-sectional study of 1-14 years old children for determination of VL prevalence rate in this age group. 1.1.4. Cohort (follow up) study of the same population for determination of the incidence rate and risk factors. 1.1.5. Investigation of LST seroprevalence rate of children in the same age group. 1.2. Investigation of reservoir. 1.2.1. Cross-sectional study of dog population (stray and pet) for determination of VL prevalence rate. 1.2.2. Follow up study of pet dogs. 1.2.3. Investigation of seroprevalence rate among dog population. 1.3. Investigation of vector. 1.3.1. Study of phlebotomus population in VL foci (determination of species, their quantity and seasonal distribution).	

	Description of deliverables
1	Questionnaire and information materials.
2	Quarterly progress report.
3	Publications.

Task 2

Task description and main milestones	Participating Institutions
2. Identification of the transmission cycle of *Leishmania* parasite. 2.1. Investigation of *Leishmania* strains isolated from humans. 2.2. Investigation of *Leishmania* strains isolated from dogs. 2.3. Investigation of *Leishmania* strains isolated from vector. 2.4. Comparison of *Leishmania* strains isolated from different sources for determination of the transmission cycle.	1 - National Center for Disease Control.

	Description of deliverables
1	Trial protocols.
2	Quarterly progress report.
3	Publications.

Task 3

Task description and main milestones	Participating Institutions
3. Improvement of laboratory diagnostic methods for VL. 3.1. Implementation of new serologic methods for detection of seropositive individuals. 3.2. Application of serologic and molecular biology methods for isolation of *Leishmania* strains and confirmation of VL diagnosis.	1 - National Center for Disease Control.

	Description of deliverables
1	Trial protocols.
2	Quarterly progress report.
3	Publication.

Task 4

Task description and main milestones	Participating Institutions
4. Development of the museum cultures of *Leishmania* species distributed in Georgia. 4.1. Culturing of *Leishmania* strains isolated during the study. 4.2. Storage of cultured strains (cryopreservation).	1 - National Center for Disease Control.
Description of deliverables	
1	Final report.

Task 5

Task description and main milestones	Participating Institutions
5. Education and training of the health personnel and scientists. 5.1. Development and publication of information/educational materials for health workers. 5.2. Training (1 course) for 15 parasitologists at NCDC Tbilisi. 5.3. Training (3 courses) of entomologists at NCDC Tbilisi. 5.4. Training (3 courses) of laboratory workers at NCDC Tbilisi. 5.5. Training (3 months) of Georgian researcher in molecular biology at NIAID, NIH, US.	1 - National Center for Disease Control.
Description of deliverables	
1	Information/educational materials.
2	Training materials.
3	Trial protocols.
4	Quarterly progress report.

5. Role of Foreign Collaborators/Partners

National Institute of Allergic and Infectious Diseases, NIH, USA, will represent foreign collaborator in this project. Within the framework of the project, the collaborators will participate in the following activities:

- jointly with colleagues from Georgia will develop questionnaires, and educational and information materials;
- will provide consultation on development of the model for epidemiological investigations;
- will assist in implementation of new tests for VL diagnosis, identification and investigation of parasite;
- will assist and consult in preparation processes of trainings and will participate in these activities;
- will train Georgian scientists in laboratories of National Institute of Allergic and Infectious Diseases;
- will participate in epidemiological and laboratory data analysis;
- jointly with Georgian scientists will prepare scientific publications;
- will provide comments to technical reports (quarterly, annual, final).

US Department of Health and Human Services/Biotechnology Engagement Program (BTEP), as a partner of ISTC, will provide financial support for the project, intended as collaboration between former weapon scientists from Georgia and scientists from USA (National Institute of Allergic and Infectious Diseases).

6. Technical Approach and Methodology

A 3 year prospective survey will be performed in new active foci of VL recently emerged in the capital of Georgia – Tbilisi that have not been investigated to date. Tbilisi is located at 500-800 m above sea level. The city has a diverse relief, divided in two parts by the river Mtkvari. The right part is higher, mostly hilly, and contains canyons and ravines; the left part is much lower and is terraced. The climate in Tbilisi is continental with an annual rainfall of 555-608 mm in low and 625-875 mm in high areas; maximum is fixed in May – 78-149 mm, and minimum in January – 19-39 mm. Heavy showers are mainly in May-June. Humidity varies from 56% to 78% depending on the area with a minimum in July-August. The warmest months are July and August with average temperature of 24-25^{0}C, and the coldest is January – 0.3-0.9^{0}C; monthly average temperature in winter is 1.8^{0}C, in spring – 11.4^{0}C, in summer – 22.7^{0}C, and in autumn – 13.6^{0}C.

The city officially is divided into 10 raions (each includes several micro-raions):

1. Krtsanisi (Ponichala, Krtsanisi, Ortachala, part of Sololaki).
2. Mtatsminda (Mtatsmindisubani, parts of Vake, Vere, and Saburtalo).
3. Vake (parts of Vake, Vere, and Saburtalo).
4. Saburtalo (part of Saburtalo, Didi Digomi, Vashlijvari).
5. Didube (Digomi, Didube).
6. Gldani (Avchala, Gldani, Mukhiani, Temka, part of Sanzona).
7. Nadzaladevi (part of Sanzona, Nadzaladevi, Lotkini).
8. Chugureti (Kukia, Svanetisubani, Kukia).
9. Isani (Avlabari, part of Navtlugi).
10. Samgori (part of Navtlugi, Vazisubani, Varketili, Lilo).

Active foci of VL are districts situated in woody piedmont areas in the old part of Tbilisi – Mtatsminda, Vake, Krtsanisi; although sporadic cases are registered in other further districts – Isani, Saburtalo, Gldani, Nadzaladevi, Didube, Chugureti, Samgori. Houses in old part of the city are two- or three-storied, built from bricks or cement blocks with courtyards where domestic animals and poultry are kept. Density of the population in these areas is high. These populated areas are closely bordered by undeveloped land left in its natural state, covered by mixed forest with deciduous and coniferous trees (poplar, asp, birch, oak, maple, lime, bird cherry-tree, chestnut, acacia, ash-tree, sequoia, fir, cedar, pine-tree, spruce etc.) and bushes (vine, ivy, bay-tree, box-tree, barberry, hawthorn, dog-rose, sea-buckthorn, jasmine, lilac, oleander, bamboo etc.). The same plants are distributed within the city as well. Large areas inside and outside of the city are occupied by orchards, fields and vegetable gardens. The slope of Mtatsminda Mountain and bordering territories, on which are located the main VL foci, consist of gray-brown clay soil.
Selection of human and dog population for investigation will be confined by areas (streets), where are located most of leishmaniasis cases registered during the last 8 years (1997-2004). These areas will be separated in the three main foci according to official borders of the city raions.
Focus I – in Krtsanisi raion, bordered by Krtsanisi, Gorgasali, Asatiani streets, and suburb.

Human population – 27 047.

Children of 0-14 age group – 5 155.

Focus II – in Mtatsminda raion, bordered by Asatiani Dadiani, Rustaveli, Barnov, Kekelidze streets, and suburb.

Human population – 43 133.

Children of 0-14 age group – 8 914.

Focus III – in Vake raion, bordered by Barnov, Shanidze, Melikishvili, Chavchavadze, Tamarashvili streets, and suburb.

Human population – 27 053.

Children of 0-14 age group – 6 855.

1. Investigation of population.
The choice of appropriate approaches for one or another epidemiological investigation always remains as a subject for discussions. Many authors compare cohort and case-control studies, show their advantages and disadvantages *[9, 14, 31, 33]*.
Case-control studies are much less expensive and much quicker to perform than cohort studies. The main problem of case-control studies is their vulnerability to systematic bias. The reasons are related to two characteristics: first, the groups to be compared are selected by researcher and are not constituted naturally;

second, the exposure is measured after the disease has already occurred. Consequently, risk or disease frequency cannot be measured directly, relative risk of exposure can be assessed by odds ratio.
In cohort studies risk and the frequency of disease as well as relative risk can be measured directly. Thus, cohort studies allow to reveal exposure to possible risk factor avoiding systematic bias that arises certainly when exposure is measured after outcome was happened. As presence of connection during the time between probable cause and outcome serves as an important criterion for evaluation of cause-and-effect relationship, cohort studies assure the stronger basis for such evaluation. The main disadvantage of this method is associated with the losses for follow-up that are likely to occur when participants must be followed for months or years. Despite there is nearly universal agreement that cohort study can provide valid evidence and, if feasible, is the design of choice *[9]*.
Thus, selection of one design over another should be made on the basis of the particular hypothesis being tested, the resources available, and the current state of knowledge. It should be considered such factors as nature and features of studied disease, characteristics of studied population, objectives of investigation, data are expected to be obtained, and purposes these data will be used for in the future.
In case of leishmaniasis investigation in new emerging foci in Tbilisi, the following circumstances should be taken into account:

- there is a lack of information about the frequency and characteristics of the disease in studied foci;
- there are no data for today on modifiable factors that determine such increase of disease in given foci;
- there are no simple and accurate methods for diagnosis of leishmaniasis, as a result increase of subclilical cases, incorrect diagnosis, and consequently, late or incorrect treatment may occur; detection of cases and determination of prevalence rate are urgently needed in this situation.

To collect information about the frequency and characteristics of a disease, to identify the current prevalence and distribution of disease determinants, or to determine prevalence rate of disease, there is no substitute for cross-sectional studies *[14, 31]*.
On the other hand we have assessed resources (human and financial) available in our project and considered feasible to perform cohort study. As to risk for losses in follow-up surveys, studied cohort consists of children 1-14 years old who are less subjected to migration or some other changes and have little chance to be withdrawn from the study.
Taking into account all above mentioned the cross-sectional study has been chosen for the first stage of our investigation. In order to diminish systematical bias, selection of cohort will be performed using randomization method.
Children of 1-14 age group will participate in study because about 80% of VL cases in Georgia are found in this group (due to the difficulties related to their examination children of 0-1 age group will be excluded from the study). According to data given by RIMPTM leishmaniasis incidence in target population is about 0.7%. Taking into account possible existence of subclinical, undiagnosed and misdiagnosed cases, cases registered in other health care units, or cases not registered at all, we can assume that probable incidence varies from 1.5% to 2%. Based on this assumption a sample size of approximately 4200 children will be chosen in order to detect as minimum as 70-80 children. Such sample size ensures 95% confidence interval within 0.3-0.4% of absolute error and relative error about 20%.
Cluster sampling will be used for survey. Segments, or clusters, have been chosen according to census (2002 year) enumeration areas. Each interviewer will know borders of the segment and starting point for the survey. Selection of households will be made by random walk method.
Starting point for the survey in each segment or cluster will be the first address from the list of addresses.
If the building located at the starting point is not a household (or there is no building at this address), the starting household will be the first household located according to an itinerary (we always move in right direction).
If the starting household is located in a tenement house, the first household will be chosen by the number of questionnaire that will be used for the household, more precisely, the last figure of the questionnaire number will be halved and rounded-off. For example, if the number of questionnaire that will be used for the household is 15, we will divide 5 by 2 and than round 2.5 to 3, accordingly we will choose as a starting point third household in that house. For tenement houses a sample interval will be 7, i.e. we will choose every seventh household; and for private houses this interval will be 5, i.e. we will choose every fifth household.
If the starting household is located on the border of the segment, we will move towards geographical center of this segment and will choose next household at the same side of the street according to sample interval. If the starting household is located in the geographical center of the segment, we will move along the same side of the street towards the increase of numbers of houses.

The movement will be continued according to an itinerary till following situation: 1). road is divided; 2). there is a crossroad; 3). there is a dead end; 4). there is the end of the segment; 5). there is an uninhabited territory.
If road is divided or there is a crossroad, we will write down on the pieces of paper all possible directions (except we have always been) and randomly select one of them.
If there is a dead end, or the end of the segment, or an uninhabited territory, we will turn and continue moving on the other side of the street.
In each household will be interviewed and examined all 1-14 years old children. The random walk will be finished when appropriate number of respondents will be interviewed for a given cluster.
Follow-up household surveys will be done in years 1 and 2 after the baseline survey that will assess incidence rate of VL. The same procedures for data collection will be used. Included in the survey will be the social and economic status of the family, existence of domestic animals and stray dogs in around territory. Children will be examined after consent from their parents or guardians. Children with suspected VL will be detected on the basis of questionnaire and clinical symptoms by epidemiologists and clinicians during observation. Clinical symptoms consistent with VL include persistent fever, weakness, weight loss, enlargement of liver and spleen, swelling of regional lymph nodes. Suspected cases will be referred to Tbilisi Research Institute of Medical Parasitology and Tropical Medicine for definitive diagnosis and treatment. Diagnosis will be made by microscopic detection of amastigotes in bone marrow aspirate and confirmed by parasite culture and PCR. Bone marrow aspirates will be obtained based only on the requirements for routine diagnosis, and not specifically for the purpose of the study. Only when excess aspirate is available, and following consent of parent or guardian, will clinicians be asked to provide material for parasite culture and for PCR.
Seroprevalence rates determined by rK39ELISA, and leishmanin skin test (LST) positivity rate will be determined for all children in the study cohort during the initial cross-sectional survey. Seropositivity generally indicates a recent infection (1-2 years) while LST positivity generally persists for life *[8, 23]*, thus these immunological tests will provide prevalence information regarding past or current infection by Leishmania, including sub-clinical or asymptomatic infection. Sero-conversion will be investigated in the 1 and 2 year follow-up which will provide an estimate of the incidence of new infections.
Note: Sample size calculation and census enumeration areas on maps have been provided by Department of Statistics of Georgia.

2. *Investigation of reservoir.*

As it is well known canids represent reservoir for visceral leishmaniasis *[22, 23, 26, 29, 30, 34, 39]*. Dogs are believed to play important role in human VL and the prevalence of canine infection rates ranges from 1.1% to 37% in different countries *[29]*. The domestic cycle takes place in pet dogs, and a peridomestic cycle is maintained in stray dogs and wild canids, which has progressive synanthropy (association with humans and their dwellings) *[26]*. Thus, routine diagnosis of canine leishmaniasis by accurate and sensitive methods is important for monitoring VL transmission in a given territory and, thereby, is essential for VL surveillance *[34]*. In a recent paper Haydon at al. discuss the practical value of different approaches that may be used to identify reservoirs in the field. According to this discussion when emerging diseases first appear, only rapid, accurate identification of the reservoir will enable appraisal of the full range of disease-control options *[13]*.
In many cases, infected dogs not presenting classical signs of VL (asymptomatic) have represented up to 50% of seropositive dogs identified in field surveys. Asymptomatic dogs have been found to harbor parasites for as long as 25 months, and importantly, they appear to be as infective to the sand fly vector as symptomatic dogs *[1, 10, 24, 27]*. The most widely used method for epidemiological investigation of canine VL is detection of parasite-specific antibodies in serum samples. This method is non-invasive and sensitive in about 70% cases of VL in dogs with clinical symptoms. However, according to data from endemic countries, infected, asymptomatic dogs often remain seronegative or borderline positive. Thus, it appears that serology is not always a good indicator of infection and there is a need for additional methods. During the past several years many authors have shown that using PCR on bone marrow aspirates or on peripheral blood can significantly improve parasite detection *[18]*. In one study *[19]*, prevalence was found to be 79.8% by PCR compared with 29.6% by serology; 89.4% of symptomatic and 65.2% of asymptomatic dogs harboured parasites in peripheral blood.
Based on such crucial role of canines in the typical transmission cycle of zoonotic VL caused by *L. infantum*, it is necessary to investigate the dog population (pet and stray) in and around the emerging foci in Tbilisi. A determination of the prevalence of canine VL will be paramount for timely implementation of control measures and prevention of spreading of the disease.

Both domestic and stray dogs will be included, since in endemic regions with a large stray dog population the strategy of targeting only domestic dogs may not be enough *[5]*. While we do not know the size of the domestic and stray dog populations in the proposed study area, there is an estimated about 15-18 thousand domestic and 15-20 thousand stray dogs in Tbilisi.

As there is a total lack of information about leishmaniasis prevalence in dog population in Georgia and such kind of surveys have never been done, the first survey to be completed in the first year will be cross-sectional. Approximately 600 domestic dogs, 200 for each focus, will be tested in the cross-sectional study. Follow-up surveys will be done in years 2 and 3 to assess incidence rate of VL or asymptomatic infection in domestic dogs.

Different situation is for stray population. Because of extensive migration of stray dogs through the city and their location in the suburbs as well as high level of lethality, it seems to be impossible to track cohort in limited territory, especially in follow–up studies. Due to such circumstances and existence of human leishmaniasis cases in other parts of Tbilisi as well, we decided to study stray dog population in all raions and suburbs of the city. The more so as such kind of survey have never been performed and we have opportunities to obtain results that will give the true picture of leishmaniasis prevalence in canine population of Tbilisi. Presumably, at least 700 dogs, 70 for each raion, will be studied in cross-sectional survey for the first year. These results will give preliminary data to estimate representative sample size for the next two years.

For domestic dogs, sample collection will be done after consent from owners. Prior to sampling, all dogs will be examined for typical clinical signs of canine VL (including swelling of popliteal lymph nodes). Dogs will be anesthetized (intramuscular injection of 2% acepromazine) for sample collection. Peripheral blood and bone marrow will be collected for the study. Peripheral blood (at least 2 ml) will be collected from a femur or foreleg vein, centrifuged on the same day, and stored at -20^0C for further examination. The bone marrow aspirate will be obtained by puncturing the iliac crest and stored in the same manner. Dogs will be marked with collars for further identification. VL will be confirmed by presence of amastigotes detected microscopically in smears of bone marrow aspirate, serology and PCR analysis. Serological study will be performed by rK39ELISA. Finally, to also confirm the species and zymodeme identity of the canine isolates, DNA from bone marrow and/or peripheral blood samples will be investigated by PCR.

3. Investigation of vector.

Some 14 species of *Phlebotomus* sand flies were reported from the eastern part of Georgia. *P. papatasi* of the subgenus *Phlebotomus; P. caucasicus, P. mongolensis, P. sergenti and P. jacusieli* of the subgenus *Paraphlebotomus; P. kandelakii, P. tobbi, P. major syriacus, P. transcaucasicus and P. wenyoni* of the subgenus *Larroussius;* and *P. simici, P. halepensis, P. chinensis tauriae, and P. balcanicus* of the subgenus *Adlerius*. Members of the subgenus *Larroussius* represent the most important vectors of *Leishmania infantum* in southern Europe *[15]*. In the former USSR, members of the subgenera *Larroussius* and *Adlerius* were suspected as vectors of *L. infantum*, none were incriminated *[15]*.

Studies on the distribution, seasonality and behaviour of sand flies in disease foci in Georgia have not been carried out for the past 14 years. Early studies indicate that the sand fly season begins in April and ends towards mid October. In VL foci in Georgia, *P. kandelakii, P. balcanicus and P. sergenti* are the predominant species, with *P. kandelakii* being the most abundant. The species are monovalent, peaking at the end of July for *P. kandelakii* and *P. balcanicus* and in mid August for *P. sergenti [11]*.

Considering the significant changes that have occurred in Georgia in the past decade, and the emergence of new foci of VL, entomological investigations are urgently indicated to identify the vector/s responsible for the transmission of *L. infantum* to man and dog. This will be achieved through the following action items:

Year 1-2

- Determine the species prevalent in active foci of VL in Tbilisi: Traps (mainly sticky paper traps, light traps and aspirators) will be placed in peridomestic and sylvatic niches considered suitable resting sites for sand flies. These include inhabited houses, sheds of domestic animals and poultry, tree holes in the surrounding forest, burrows and caves of wild animals. Traps will be placed at dusk and collected at dawn. This will be done once every two weeks over a period of 2 consecutive days for the duration of the sand fly season. The captured sand flies will be identified using a collection of taxonomic keys. The collection site and feeding status (blood fed or not) of each fly will be registered. This data will show the prevalent *Phlebotomus* species in the study sites, their resting (exo-endophily) and feeding (exo-endophagy) behaviour.

- Identify the source of blood from collected sand fly specimens: This will be carried out using a dot blot assay against human and dog sera.
- Identify sand flies feeding on dogs via animal baits: Once every 2 weeks, dogs will be placed in cages inside a tent for a period of 2-3 hours during peak sand fly activity. Flies entering the tent will feed on the caged dog and rest on the inner walls of the tent where they will be easily captured and identified.

Collectively, the above mentioned preliminary studies will point to potential vectors of *L. infantum* for humans and dogs and will aid in determining the best approach for their incrimination and control.

Year 2-3

- Incriminate suspected vectors by finding parasites in captured sand fly specimens. This will be carried out towards the end of the sand fly season when the infection rate is highest in the population. Following the identification of species, sand flies will be sorted then grouped in pools of fifty. PCR using primers specific for *L. infantum* (see PCR below) will be performed on these pools for incrimination of the vector/s. Dissection of individual flies from chosen trip collections will also be carried out to get an accurate estimate of the infection rate in these flies.

We need to perform the dissection of individual Phlebotomus specimen since:1. Tbilisi has several species that may act as vectors and that will have a defined vector status, e.g. due to feeding habits and infection rates. Pooling of specimens will mask which species is infected and will mask the rate of infection in each species.2. Dissection of individual specimens will provide a more sensitive and accurate assessment of the rate of infection in each species compared to pooling of 50-100 flies.3. Finding infected flies will result in the isolation, growth and storage of the parasite strain from the fly. This is important as further characterization of the parasite may be needed, particularly for comparison with strains isolated from humans and dogs.4. The dissection of the midgut, identification of the species, and examination under the microscope for infections is straightforward and rapid. 5. It is comparable to the time needed for the isolation of DNA from individual flies if PCR is considered for each specimen, but is much cheaper and provides an immediate answer.

The number of sand flies to be collected will depend on their density during the time of collection. We need to carry out a monthly collection for one year. This is very important as:

1. It will determine the season and the most likely time of peak transmission.
2. It is necessary because in Tbilisi, as it mentioned above, there are several potential vector species and their seasonality may vary where one species may be a primary vector at one time and others may act as secondary vectors at another, i.e. their seasonality will not necessarily be the same.
3. Some species have only one seasonal peak but others may have 2 peaks and therefore, two times where transmission can potentially peak.

Doing an annual survey is well justified and will be carried out in a delimited area of high incidence of cases; it is not overly exhaustive of resources and will result in the necessary training of 1 or 2 local entomologists for long term purposes.

The collected sand flies will be identified, and the bloodmeal of engorged females of the same collected specimens will be analyzed. Bloodmeal analysis may be done at defined time points, eg at the beginning, peak and end of season, to monitor any changes in the feeding behaviour of vectors. Moreover, this test is an ELISA where a large number of samples can be run at one time and the bloodmeal will be dried on filter paper and so could be analyzed when suitable. Bloodmeal analysis will define the species that feed on both dogs and humans, those that feed primarily on dogs etc. and provide important information regarding vector status. Furthermore, it should be noted that the number of collected sand flies will be small at the beginning and towards the end of the season, and the time needed for specimen processing will be considerably decreased.

As for infection rates being low, that is true overall, however, if the transmission cycle is very focal, as is probably the case in Tbilisi, where there is urban transmission and the fly, dog and human are in close contact, that may not be the case. Moreover, we know the reservoir and trapping sand flies that are feeding on, and resting around dogs may enrich the collection of infected specimens. Also, towards the end of the peak abundance when the sand fly population is old and not diluted by numerous newly emerged flies, the likelihood of finding infected flies increases significantly. We will use the appropriate approach to identify infected sand flies based on their species diversity in collections and on their numbers.

Analysis of epidemiological data will be performed using EPIINFO (CDC, Atlanta, GE, USA) and SPSS programs.

Laboratory methods that will be used for detection of infected individuals and dogs, and for identification of *Leishmania* strains.

At present different laboratories use various methods and their combination for diagnosis of VL, for detection of infected or exposed individuals, and for species typing of *Leishmania*. There is no one method that does not have some limitation. Classic methods such as microscopic examination of Giemsa stained smears of bone marrow, liver, or spleen, and/or culture of these specimens or peripheral blood, confirm VL in about 80% of the cases. But these methods require a large amount of parasites in the sample and invasive intervention. Sensitivity is often decreased because of possible culture contamination. Moreover, complexity of invasive procedures makes these techniques difficult to repeat for follow-up patients *[5, 32, 36]*. Methods involving the use of monoclonal antibodies, isoenzyme and schizodeme analysis, and DNA hybridization, are long and complicated, and require large volumes of cultured parasites *[20, 32]*. Current immunological methods for detection of parasite-specific antibodies in serum – IFAT, DAT, ELISA – also have disadvantages *[3, 29, 36, 40]*. Often they are not always sensitive enough to pick up sub-clinical or asymptomatic infections, they may not distinguish between past and present infection, and they do not work in immunocompromised patients. Furthermore, they are not useful for parasite species identification. A majority of investigators give preference to ELISA as the most sensitive serological test for VL and for detection of infected individuals, although many researchers consider DAT as equally reliable.

In the recent years many authors give preference to the use of rK39 antigen for serodiagnosis of VL *[4, 16, 28, 40]*. As has been shown by Zijlstra et al., rK39 ELISA proved more sensitive than DAT in diagnosis of patients with leishmania infection in Sudan (93% and 80%, respectively); both tests remain positive up to 24 months after treatment. In individuals with subclinical infection rK39 ELISA could detect infection 6 months earlier in ~40% of patients in comparison with DAT *[40]*.

rK39 is the cloned antigen of 39 amino acid repeats of a kinesin-like gene found in *L. chagasi*. Antibodies to rK39 antigen could be detected by ELISA in nearly 98% of sera from patients with VL in Brazil, Sudan, China and Pakistan *[16, 40]*. 100% specificity and 97% sensitivity has been shown by some researchers in case of canine leishmaniasis *[28]*.

It was suggested that the presence or absence of antibodies to rK39 may predict progression to VL or self-healing, respectively *[40]*. Anti-rK39 antibody titers were found to correlate with parasite burden and may be useful in evaluating the result of chemotherapy. With successful therapy, the anti-rK39 antibody titers declined steeply at the end of treatment and during follow-up. In contrast, patients who relapsed showed increased titers of antibodies to rK39. The extremely high levels of anti-rK39 antibodies in VL cases suggest the application of rK39 for sensitive and specific serodiagnosis, and rK39 ELISA is also valuable in monitoring drug therapy and detecting relapse of the disease *[16]*.

The use of molecular-biology methods, particularly PCR, for diagnosis of VL and investigation of parasite strains, has a number of advantages. Numerous studies have shown that PCR is a very sensitive and specific method for detection of *Leishmania* DNA in different clinical samples from human, dogs, and foxes *[36]*. PCR can be performed in any biological sample, and at present time is used as standard diagnostic approach in many laboratories *[29, 36]*. With the use of appropriate primers combined with analysis of the size of the amplified product, PCR has the advantage of being able to identify species or sub-species of *Leishmania*, and determining the relationship between isolates, for example between affected humans and dogs. A potential draw back of the method is the requirement for biopsies of tissues harboring parasites, such as spleen or bone marrow. Only a few authors have described high sensitivity of PCR used on peripheral blood, explained by relatively low levels of blood parasitemia as well as difficulties usually encountered in the PCR performed with blood-containing samples. Steuber et al. reported high positivity both in blood (87%) and bone marrow (100%) *[37]*. And according to Lachaud et al., PCR was able to detect 1 to 10 parasites/ml of blood that made it possible to confirm the diagnosis of VL in 99% of cases, including early diagnosis during relapses. But PCR was not able to identify healthy carriers *[17]*.

There are several papers in the literature showing the application of either a single protocol or a combination of two or more protocols to answer basically the same kind of questions: whether the very same parasite is found in reservoirs, vectors and human in a number of outbreaks; or whether these techniques are sensitive enough to be used in those cases. And as far as sensitivity, these techniques have been shown to be very sensitive and reliable.

The random amplified polymorphic DNA (RAPD) technique uses random oligomers to amplify genomic DNA. In the case of *Leishmania*, RAPD studies mostly aimed to assess the technique to establish and estimate of the genetic relationship among sets of taxa, species, and isolates. For instance, Guizani et al. *[12]* used RAPD to identify and differentiate several species of Old World *Leishmania* (*L. infantum, L. donovani, L. major, L. tropica, L. turanica, L. arabica, L. aethiopica, L. killicki*) and one species from the New World (*L. chagasi*). The primers used, although useful for separating between parasites causing cutaneous from the ones causing visceral disease, could not distinguish parasites from the donovani complex (*L. donovani, L. infantum, L. chagasi*).

As for RFLP, the technique is based on the DNA amplification using primers deriving from the conserved regions of the mini-exon gene, and a later restriction enzyme digestion of the amplified product to produce restriction fragment length polymorphism (RFLP) profiles. This technique shows excellent reproducibility and high degree of reliability; it is also remarkably simple and rapid in compare with isoenzyme typing *[21, 25, 39]*.

A recent paper by Marfurt at al. *[21]* shows the use of RFLP in genotyping Old and New World *Leishmania*. These authors used primers to amplify a fragment of the mini exon gene and upon digestion with several restriction enzymes, noted that, with at least one enzyme (EaeI), the profile of digested mini-exon PCR products could differentiate members of the *Leishmania* subgenus in a species-specific manner. Similar protocols can be used in our case to analyze samples obtained from patients, dogs and even sand flies. No need for parasite isolation through culture is necessary, since this assay is sensitive for crude extracts as well. However, according to Marfurt et al. *[21]* a limiting factor in such assay relates to the number of parasites present in a given sample. For parasites of the *Viannia* subgenus, as little as 10 organisms is sufficient, whereas for parasites of the *Leishmania* subgenus the number is approximately 50. Such discrepancy seems to be associated with the size of the PCR obtained as wel as the apparent higher copy number of mini-exon sequences in *Viannia*. The same primer sets described by Marfurt et al. *[21]* could be used in our investigation and, in addition, a primer set based on the kDNA of *L. major* and named Uni21 and Lmj4 *[2]* can also be applied. The PCR products would be digested with various restriction enzymes and separated on either agarose or acrylamide gels, depending on their predicted sizes.

In a very recent paper, Schnur at al. *[35]* used RFLP of kDNA PCR products to study a *L. tropica* outbreak in the Judean desert. Using the primers described by Anders et al. *[2]*, followed by restriction enzyme digestion, they showed that for a human case of CL caused by *L. tropica*, the parasite differed from the parasite found in sand flies. In addition, these authors applied SSCP (single strand conformation polymorphism) analysis of the ITS (internal transcribed spacer) of the ribosomal operon (by using a primer set specific for the ITS), which was able to separate the *L. tropica* from the *L. infantum* and *L. major*. Depending on the necessity, a similar strategy based on SSCP can be applied in our system.

Finally, direct sequencing of PCR products can also be used to identify potential differences in different isolates.

Taking into account the need to investigate many aspects of VL in Georgia including disease and infection prevalence in humans and dogs, species and zymodeme analyses of isolated strains, identification and confirmation of links in transmission cycle, it will be necessary to make use of a combination of the following methods:

- **Microscopic examination of Giemsa stained smears of bone marrow.**
- ***In vitro* cultivation.**
- **Cryopreservation of isolated strains.**
- **LST (Leishmanin Skin Testing).**
- **rK39 ELISA (Enzyme Linked Immunosorbent Assay).**
- **PCR (Polymerase Chain Reaction).**
- **PCR-RAPD, PCR-RFLP, ITS-SSCP techniques.**

As it was mentioned earlier, at NCDC, owing to financial support granted for different projects, were successfully implemented the new methods such as ELISA or PCR by means of that is carried out diagnosis of amebiasis, botulism and some other infectious diseases as well as investigation of causative agents and their resistance to antibiotics. Introduction of newest serological and molecular biology techniques will strengthen even greater laboratory capability in Georgia; on the other hand it will reduce undiagnosed, diagnosed but untreated, or inadequately treated cases, and contribute to development of appropriate control measures in order

to reduce incidence. Hence, these results will meet the major public health objectives that include primary and secondary prevention of disease.

Education and training of the health personnel.

Project participants from NCDC, NIAID and institute of parasitology will jointly develop information and educational materials for VL, which will be printed in the form of booklets and leaflets. They will be distributed to various medical institutions and clinics, and health professionals throughout Georgia.

15 parasitologists will participate in training that will be conducted by trainers from NCDC and institute of parasitology.

Partners from NIAID will conduct several short *in country* courses for 10 entomologists and 5 laboratory workers.

One senior Georgian researcher will be trained (for 3 months) in molecular biology laboratories of NIAID in order to cope with molecular-biology technique.

7. Technical Schedule

	Quarter 1	Quarter 2	Quarter 3	Quarter 4	Quarter 5	Quarter 6	Quarter 7	Quarter 8	Quarter 9	Quarter 10	Quarter 11	Quarter 12	Person*days
Task 1	Questionnaire and information materials	Quarterly progress report	Quarterly progress report	Publication	Quarterly progress report	Quarterly progress report	Quarterly progress report	Publication	Quarterly progress report	Quarterly progress report	Quarterly progress report	Publication	
Person*days	563	493	497	493	497	493	497	493	497	493	497	493	**6006**
Task 2			Quarterly progress report	Trial protocols		Publication	Quarterly progress report	Trial protocols		Quarterly progress report	Trial protocols	Publication	
Person*days	78	77	78	77	78	77	78	77	78	77	78	77	**930**
Task 3			Trial protocols	Quarterly progress report	Publication		Trial protocols	Quarterly progress report			Trial protocols	Publication	
Person*days	89	87	89	87	89	87	89	87	89	87	89	87	**1056**
Task 4												Final report	
Person*days	88	87	88	87	88	87	88	87	88	87	88	87	**1050**
Task 5	Information materials	Training materials		Training materials		Training materials		Quarterly progress report		Training materials		Quarterly progress report	
Person*days	117	116	117	116	117	116	117	116	117	116	117	116	**1398**
TOTAL	935	860	869	860	869	860	869	860	869	860	869	860	**10440**

8. Personnel Commitments.
8.1. Individual participants.
Leading Institution: NCDC.
Category I (weapon scientific and technical personnel)

Name	Birth Year	Scientific Title	Weapon Expertise Ref.	Function in project	Daily rate (US$)	Total days	Total grants (US$)
Giorgobiani Ekaterina	1957	Cand. of Biol. Scien.	3.4	Project manager, coordination and supervision all activities through the project.	35	618	21630
Kurtsikashvili Levan	1930	Cand. of Med. Scien.	3.4	Principal Investigator, scientific consultation.	30	420	12600
Iosava Merab	1963	MD	3.4	Member of epidemiologists group, epidemiological investigation, preparation of questionnaires and educational materials, cluster survey, serosurvey.	24	210	5040
Tushishvili Tsiuri	1959	MD	3.4	Member of epidemiologists group, epidemiological investigation, preparation of questionnaires and educational materials, cluster survey, serosurvey.	25	576	14400
Chogovadze Tamara	1971	MD	3.4	Member of epidemiologists group, epidemiological investigation, preparation of questionnaires and educational materials, cluster survey, serosurvey.	24	120	2880
Zedginidze Yulia	1957	MD	3.4	Member of epidemiologists group, epidemiological investigation, preparation of questionnaires and educational materials, cluster survey, serosurvey.	25	288	7200

Machablishvili Anna	1977	MD	3.4	Member of epidemiologists group, epidemiological investigation, preparation of questionnaires and educational materials, cluster survey, serosurvey.	25	288	7200
Dolidze Natalja	1962		3.4	Member of entomologists group, entomological investigation, vector collection, preparation, differentiation and identification of *Phlebotomus* species.	30	360	10800
Shalutashvili Irakli	1942		3.4	Member of zoologists and veterinarians group, epidemiological investigation of reservoir, dogs examination and anesthetization.	24	270	6480
Kikaleishvili Konstantin	1950		3.4	Member of zoologists and veterinarians group, epidemiological investigation of reservoir, dogs examination and anesthetization.	24	270	6480
Mamatsashvili Tamara	1971		3.4	Member of laboratory group, assistance in laboratory diagnostics, isolation and cultivation of *Leishmania* strains.	24	180	4320
Grdzelidze Marina	1950	MD	3.4	Member of laboratory group, cryopreservation of isolated *Leishmania* strains.	24	270	6480

Berulava Archil	1955	Cand. of Biol. Scien.	3.4	Member of laboratory group, scientific investigation, immunological and molecular biological analysis of isolated *Leishmania* strains.	32	642	20544
Chanturia Gvanca	1972	Master in Biol. Scien.	3.4	Member of laboratory group, scientific investigation, immunological and molecular biological analysis of isolated *Leishmania* strains.	24	330	7920
Chitadze Nazi	1977	Master in Biol. Scien.	3.4	Member of laboratory group, scientific investigation, immunological and molecular biological analysis of isolated *Leishmania* strains.	24	330	7920
Bokeria Ketino	1964		3.4	Member of computer service group, assistant in computer operation, data analysis.	20	216	4320
					Total:	**5388**	**146214**

Category II (other scientific and technical personnel)

Name	Birth Year	Scientific Title	Function in project	Daily rate (US$)	Total days	Total grants (US$)
Chubabria Giorgi	1937	Doct. of Med. Scien.	Member of laboratory group, consulting in laboratory diagnosis, patients monitoring, preparation of questionnaires and educational materials, training of medical personnel.	25	432	10800
Gugushvili Guguli	1924	Doct. of Biol. Scien.	Member of entomologists group, entomological investigation, vector collection, preparation, differentiation and identification of *Phlebotomus* species.	25	288	7200
Babuadze Giorgi	1981		Member of entomologists group, entomological investigation, vector collection, preparation, differentiation and identification of *Phlebotomus* species.	25	432	10800
Daraselia Temur	1955		Member of zoologists and veterinarians group, epidemiological investigation of reservoir, samples collection, serosurvey of dogs.	20	324	6480

Badashvili Goderdzi	1957	MD	Member of zoologists and veterinarians group, epidemiological investigation of reservoir, samples collection, serosurvey of dogs.	20	324	6480
Zenaishvili Otar	1924	Doct. of Med. Scien.	Member of clinicians group, consultation in clinical work, patients' examination and monitoring, bone marrow samples collection.	25	432	10800
Iashvili Nino	1963	MD	Member of clinicians group, preparation of questionnaires and educational materials, people examination in *Leishmania* foci, serosurvey.	20	324	6480
Makharadze Manana	1948	MD	Member of clinicians group, preparation of questionnaires and educational materials, people examination in *Leishmania* foci, serosurvey.	20	324	6480
Zakaraia Tsiuri	1950	MD	Member of clinicians group, preparation of questionnaires and educational materials, people examination in *Leishmania* foci, serosurvey.	20	324	6480

Mandjgaladze Marina	1960	MD	Member of clinicians group, preparation of questionnaires and educational materials, people examination in *Leishmania* foci, serosurvey.	20	324	6480
Broladze Medeja	1957	MD	Member of clinicians group, preparation of questionnaires and educational materials, people examination in *Leishmania* foci, serosurvey.	25	432	10800
Namoradze Guliko	1928	MD	Member of epidemiologists group, preparation of questionnaires and educational materials, training of medical personnel.	25	150	3750
				Total:	**4110**	**93030**

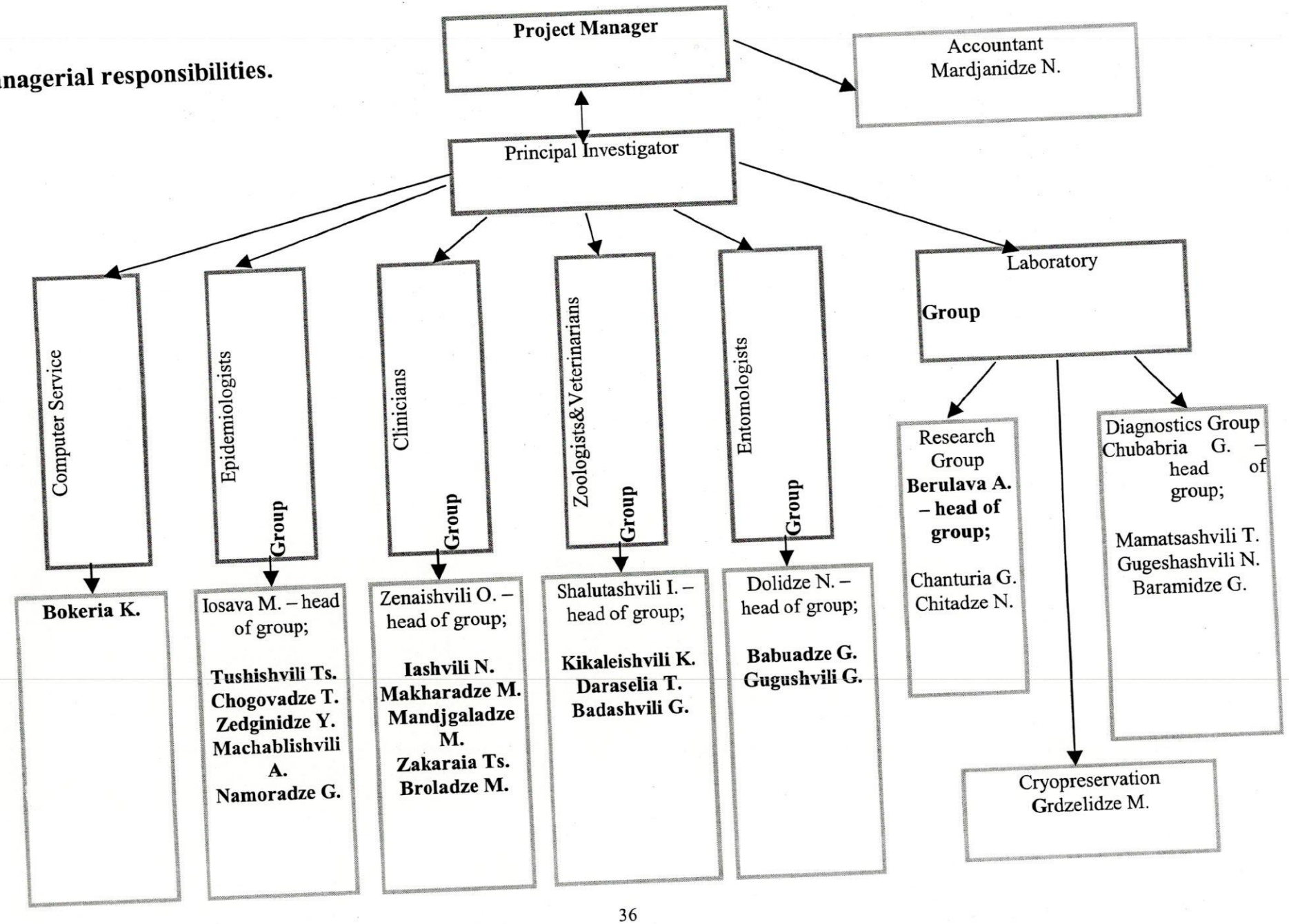
Category III (Participant personnel)

Name	Birth Year	Function in project	Daily rate (US$)	Total days	Total grants (US$)
Baramidze Gvritia	1940	Member of laboratory group, technical personnel in laboratory diagnostics, media preparation.	15	384	5760
Gugeshashvili Nadezhda	1942	Member of laboratory group, technical personnel in laboratory diagnostics, media preparation.	20	180	3600
Mardjanidze Nana	1974	Accountant, accounting for project activities.	20	180	3600
			Total:	**744**	**12960**

Category IV (personnel, who will work less than 10% of project duration)

Number of persons	Function in project	Daily rate (US$)	Total days	Total grants (US$)
1	Consultation in study design.	10	66	660
2	Technical service.	10	132	1320
		Total:	**198**	**1980**

8.2. Managerial responsibilities.



9. Financial Information

TABLE 1

Estimated Aggregated Expenditures by Recipient

Category	Quarters 1 & 2		Year 1		Year 2		Year 3		Total	
	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)
1 Grant Payments:										
1.1 Category I		24369		48738		48738		48738		146214
1.2 Category II		15505		31010		31010		31010		93030
1.3 Category III		2160		4320		4320		4320		12960
1.4 Category IV		880		1100		440		440		1980
Total Grant Payments		**42914**		**85168**		**84508**		**84508**		**254184**
2 Equipment:										
2.1 Capital Equipment		17010		17010						17010
2.2 Non-Capital Equipment		10872		10872						10872
Total Equipment		**27882**		**27882**						**27882**
3 Materials/Supplies		**58126**		**58126**		**9225**		**1111**		**68462**
4 Bank Fees	**45**	**1340**	**66**	**1970**	**20**	**1040**	**30**	**856**	**116**	**3866**
5 Other Direct Costs:										
5.1 Technological Energy							504		1512	
5.2 Communications	252		504		504		960		2880	
5.3 Subcontracts/Seminars	480	5060	960	5060	960	1600		400		7060
5.4 Logistics/Customs							600		5475	
5.5 Other	3750		4275		600					
Total ODC	**4482**	**5060**	**5739**	**5060**	**2064**	**1600**	**2064**	**400**	**9867**	**7060**
6 Travel:										
6.1 Internal ***	1000		1000				1000		2000	
6.2 Outside CIS				19850		9200				29050
Total Travel	**1000**		**1000**	**19850**		**9200**	**1000**		**2000**	**29050**
Overhead/Retainage									**11787**	
Subtotals	**5527**	**135322**	**6805**	**198056**	**2084**	**105573**	**3094**	**86875**	**23770**	**390504**
Totals	**140849**		**204861**		**107657**		**89969**		**414274**	

Remarks: * (1) - Cash flow through Recipient Account
** (2) - Cash flow through ISTC
*** Include Local and inside CIS travel

10. Equipment and Materials Summary

10.1. Equipment Summary

TABLE 2

EQUIPMENT/MATERIAL SUMMARY

EQUIPMENT SUMMARY

for Project Agreement #G-1081

To be provided in kind [X]
To be purchased by recipient [ ]

The ISTC will normally provide the most appropriate equipment that will perform the functions required; however, if very special reasons are given and explained in detail (Form PR-2E), the purchase of a particular make will be considered.

Please list items in the order of their priority and put an 'X' in the column next to "Item no." if ISTC form PR-2E, "Data for a Single Equipment Item', has been completed for a given item and is attached.

Item No.		DESCRIPTION OF ITEM	Date needed (quarter)	Qty	Unit cost (USD)	Amount (USD)
Leading Institution: NCDC						
		Capital equipment				
1		Labotect Cryo Unit, Labotect, 9030	1	1	13365.00	13365.00
2		Cryosistem 2000 Labotect, 325234	1	1	3645.00	3645.00
		Non-capital equipment				
3		Gloves (M) Labotect, 325010	1	1	224.00	224.00
4		Short Range Projector, Palmer Cap-Chur Equipment, 1400	1	2	184.00	368.00
5		Fold-Down Cages, ACES, FD-205	1	2	100.00	200.00
6		Xcell SureLock Mini-Cell w/ blot module, Invitrogen, EI0002	1	1	772.00	772.00
7		Mini electrophoresis Power supply, Thomas Scientific, 4314B50, model EC105	1	1	560.00	560.00
8		Primo EC330 Midicell gel system, Thomas Scientific, 4313F03	1	1	453.00	453.00
9		Primo EC340 Maxicell gel system, Thomas Scientific, 4313F08	1	1	530.00	530.00
10		New Standard Miniature Light Trap - Model 1012, John Hock, 1012	1	15	143.00	2145.00
11		Automatic charger for two 6 Volt batteries, input voltage of 220 AC, John Hock, 2.88-6V-220	1	8	202.00	1616.00
12		Notebook, Lifebook S7010, Fujitsu-Siemens, Alta Ltd.	1	1	2240.00	2240.00
13		Computer, Pentium-IV, Fujitsu-Siemens, Alta Ltd.	1	1	707.00	707.00
14		Computer, Pentium-IV, Fujitsu-Siemens, Alta Ltd.	1	1	810.00	810.00
15		Printer, Canon Laser LBP-3200, Alta Ltd.	1	1	247.00	247.00
					Subtotal:	**27882.00**
					Estimated TOTAL COST:	**27882.00**

Form PR-1E of 3/98

10.2. Materials Summary

TABLE 3

EQUIPMENT/MATERIAL SUMMARY

MATERIAL SUMMARY

for Project Agreement #G-1081

To be provided in kind [X]
To be purchased by recipient [ ]

The ISTC will normally provide the most appropriate equipment that will perform the functions required; however, if very special reasons are given and explained in detail (Form PR-2E), the purchase of a particular make will be considered.

Please list items in the order of their priority and put an 'X' in the column next to "Item no." if ISTC form PR-2E, "Data for a Single Equipment Item', has been completed for a given item and is attached.

Item No.		DESCRIPTION OF ITEM	Date needed (quarter)	Qty	Unit cost (USD)	Amount (USD)
Leading Institution: NCDC						
1		96 well ELISA plate, In Bios, INE-1 (supplier A&S Ltd.)	1	44	90.00	3960.00
2		Leishmanin, Pasteur Institute of Iran, Tehran (supplier A&S Ltd.)	1,6	1000	5.00	5000.00
3		Freeze-dried DAT antigen, Royal Tropical Institute, Amsterdam (supplier A&S Ltd.)	1	65	28.00	1820.00
4		Freeze-dried DAT antigen, Royal Tropical Institute, Amsterdam (supplier A&S Ltd.)	6	60	28.00	1680.00
5		Taq PCR Master Mix Kit (1000 reactions), QIAGEN, 201445	1	2	743.00	1486.00
6		Ready-To-Go RAPD Analysis Kit (100 reactions, 6 primers), Amersham Biosciences – N27-9502-01.	1	2	970.00	1940.00
7		100 bp DNA Ladder, 50µg, Invitrogen, 15628-019	1	2	88.00	176.00
8		1 Kb DNA Ladder, 500 µg, Promega, G5711 (supplier A&S Ltd.)	1	1	101.00	101.00
9		10 mM NTP Mix, 20 µmol, Invitrogen, 18109-017	1	3	216.00	648.00
10		UltraPure™ DNase/RNase-Free Distilled Water, 10 x 500 ml, Invitrogen, 10977-023	1	5	130.00	650.00
11		Taq DNA Polymerase in storage buffer B, 100 units, Promega, M1661 (supplier A&S Ltd.)	1	5	24.00	120.00
12		Platinum® PCR SuperMix, 100 rxns, Invitrogen, 11306-016	1	3	260.00	780.00
13		BamH I,2,000 units, Invitrogen, 15201-023	1	2	50.00	100.00
14		EcoR I, 20,000 units, Invitrogen, 15202-021	1	1	173.00	173.00
15		Hind III, 10,000 units, Invitrogen, 15207-020	1	1	77.00	77.00
16		Mbo I, 200 units (10 units/µl) Invitrogen, 15248-016	1	2	100.00	200.00
17		Hinf I,1,000 units, Promega, R6201 (supplier A&S Ltd.)	1	1	46.00	46.00
18		Sma I, 1,000 units, Promega, R6121 (supplier A&S Ltd.)	1	2	66.00	132.00
19		Xba I, 2,000 units, Promega, R6181 (supplier A&S Ltd.)	1	1	60.00	60.00
20		Xho I, 10,000 units, Promega, R6165 (supplier A&S Ltd.)	1	1	126.00	126.00
21		Hae III, 2,500 units, Promega, R6171 (supplier A&S Ltd.)	1	1	62.00	62.00
22		Nco I, 200 units, Promega, R6513 (supplier A&S Ltd.)	1	1	75.00	75.00
23		Rsa I, 1,000 units, Promega, R6371 (supplier A&S Ltd.)	1	2	48.00	96.00
24		Mbo I, 200 units, Invitrogen, 15248-016	1	2	100.00	200.00
25		Ban II, 1,000u (8–12u/µl), Promega, R6561 (supplier A&S Ltd.)	1	2	94.00	188.00
26		Eae I, 100 units (3,000 units/ml), New England Biolabs, R0508S	1	6	96.00	576.00
27		Rsa I, 1,000 units (10,000 units/ml), New England Biolabs, R0167S	1	2	85.00	170.00
28		GenomicPrep™ Cells and Tissue DNA isolation kit, 55 purifications, Amersham, 27-5237-01 (supplier A&S Ltd.)	1	2	200.00	400.00
29		GenomicPrep™ Cells and Tissue DNA isolation kit, 55 purifications, Amersham, 27-5237-01 (supplier A&S Ltd.)	5	1	200.00	200.00
30		GenomicPrep™ Blood DNA isolation kit, 100 purifications, Amersham, 27-5236-01 (supplier A&S Ltd.)	1	2	200.00	400.00

31	GenomicPrep™ Blood DNA isolation kit, 100 purifications, Amersham, 27-5236-01 (supplier A&S Ltd.)	5	1	200.00	200.00
32	DNAzol Reagent, 100ml, Invitrogen, 10503-027	1	1	303.00	303.00
33	DNAzol BD Reagent, 100ml, Invitrogen, 10974-020	1	1	250.00	250.00
34	Trizol Reagent, 100ml, Invitrogen, 15596-026	1	1	308.00	308.00
35	NuPAGE 10% Bis-Tris Gel, 1mm, 15 well, Invitrogen, NP0349BOX	1	2	201.00	402.00
36	NuPAGE 4-12% Bis-Tris Gel, 1mm, 15 well, Invitrogen, NP0323BOX	1	2	201.00	402.00
37	Agarose, LE, 500g, Promega, V3125 (supplier A&S Ltd.)	1	1	570.00	570.00
38	Ethidium bromide, 10mg/ml (10ml), Invitrogen, 15585-011	1	1	58.00	58.00
39	Acrylamide for Electrophoresis, Omnipur grade, Rotiphorese Gel 40 (29:1),1000ml, ROTH, A515.1	1	1	80.00	80.00
40	Nitrocellulose Membrane (0.45um pore size), Invitrogen, LC2001	1	1	177.00	177.00
41	PVDF Membrane (0.2um pore size), Invitrogen, LC2002	1	1	177.00	177.00
42	ITS Forward primer, custom oligos 1.0 umole, HPLC purified (5'- TAT TGG TAT GCG AAA CTT CCG-3'), Sigma-genosys	1	2	110.00	220.00
43	ITS Reverse primer, custom oligos 1.0 umole, HPLC purified (5'- ACA GAA ACT GAT ACT TAT ATA GCG-3'), Sigma-genosys	1	2	110.00	220.00
44	Uni21, Forward, custom oligos 1.0 umole, HPLC purified (5'-GGG GTT GGT GTA AAA TAG GCC-3'), Sigma-genosys	1	2	110.00	220.00
45	Lmj4, Reverse, custom oligos 1.0 umole, HPLC purified (5'-CTA GTT TCC CGC CTC CGA G-3'), Sigma-genosys	1	2	110.00	220.00
46	Giemsa stain, 1L, Sigma, 48900	1	2	48.00	96.00
47	Agar-agar, 500g, Cole-Parmer, EW-88338-29	1	2	75.00	150.00
48	Sodium Chloride (NaCl), 1kg, Sigma, 71381	1	2	14.00	28.00
49	2 Mercaptoethanol, 100ml, Sigma, 516732	1	2	13.00	26.00
50	Sulfuric acid - 2.5L, Sigma, 84721	1	1	52.00	52.00
51	Dimethyl Sulphoxide, 1L, Sigma, D5879	1	1	53.00	53.00
52	SSC buffer concentrate, 10L, Sigma, 93017	1	2	193.00	386.00
53	Denhardt's solution 50xconcentrate 5x5ml, Sigma, D2532	1	1	432.00	432.00
54	Deoxyribonucleic acid, single stained salmon tested (for hybridization), 5x1ml, Sigma, D9156	1	1	176.00	176.00
55	NaOH (sodium hydroxide) 1kg, Sigma, S8045	1	1	68.00	68.00
56	HCl (hydrochloric acid) (36.5-38%), p.a., ACS, ISO 1L, ROTH, 4625.1	1	1	18.00	18.00
57	Acepromazine (pkg-50ml), Promace	1,5	220	15.00	3300.00
58	Schneider's Insect Medium, 500ml, Sigma, S0146	1	2	65.00	130.00
59	Fetal Bovine Serum, 500ml, Sigma, F9665	1	2	169.00	338.00
60	Distriman, Gilson, F164001,	1	1	294.00	294.00
61	Distri Tip Micro, 125ul, 50/box, Gilson, F164100	1	2	41.00	82.00
62	Distri Tip Micro, 1250ul, 50/box, Gison, F164110	1	3	41.00	123.00
63	Distri Tip Micro, 12,5ml, 50/box, Gilson, F164120	1	3	41.00	123.00
64	Digital multichannel micropipette Calibra® digital 852, 20-200ul, Socorex, 852.08.200 (supplier A&S Ltd.)	1	1	594.00	594.00
65	Adjustible volume micropipette Calibra® digital 822, 0.2-2ul, Socorex, 822.0002 (supplier A&S Ltd.)	1	1	218.00	218.00
66	Adjustible volume micropipette Calibra® digital 822, 10-100ul, Socorex, 822.0100 (supplier A&S Ltd.)	1	1	205.00	205.00
67	Adjustible volume micropipette Calibra® digital 822, 100-1000ul, Socorex, 822.1000 (supplier A&S Ltd.)	1	1	205.00	205.00
68	Adjustible volume macropipette Calibra® digital 832, 1-10ml, Socorex, 832.10 (supplier A&S Ltd.)	1	1	235.00	235.00
69	Workstation for 7 instruments, Socorex, 320.337B (supplier A&S Ltd.)	1	1	133.00	133.00

70		Reagent reservoir (autoclavable), 20/pkg, Socorex, 330.01 (supplier A&S Ltd.)	1	1	20.00	20.00
71		Natural ultra-microtips, 10 µl 10x96/rack 10 pack, Socorex, 309.0010FR (supplier A&S Ltd.)	1,5,9	15	203.00	3,045.00
72		Natural tips, 20 µl 10x96/rack, Socorex, 308.0020FR (supplier A&S Ltd.)	1,5	2	203.00	406.00
73		Natural extended tips, 200 µl 8x204/rack, Socorex, 308.0200LFR (supplier A&S Ltd.)	1,5	1	424.00	424.00
74		Natural tips, 1000 µl 10x100/rack, Socorex, 309.1000FR (supplier A&S Ltd.)	1,5	10	214.00	2,140.00
75		Natural ultra-microtips, 10 µl 1000/bag, Socorex, 309.0010B (supplier A&S Ltd.)	1,5	10	32.00	320.00
76		Natural ultra-microtips, 10 µl 1000/bag, Socorex, 309.0010B (supplier A&S Ltd.)	9	3	32.00	96.00
77		Natural microtips, 20 µl 1000/bag, Socorex, 302.0020B (supplier A&S Ltd.)	1	5	32.00	160.00
78		Natural superior tips, 200 µl 1000/bag, Socorex, 308.0200B (supplier A&S Ltd.)	1	20	33.00	660.00
79		Natural superior tips, 200 µl 1000/bag, Socorex, 308.0200B (supplier A&S Ltd.)	5	5	33.00	165.00
80		Volac Pasteur Pipettes, 1.5ml, 1000/pkg, Cole-Parmer, EW-25554-00	1	2	45.00	90.00
81		Volac Pasteur Pipettes, 2.0ml, 1000/pkg, Cole-Parmer, EW-25554-00	1	2	50.00	100.00
82		Measuring Pipettes, 2.0ml, 12/cs (reusable), Cole-Parmer, EW-25562-12	1	2	95.00	190.00
83		Measuring Pipettes, 5.0ml, 12/cs (reusable), Cole-Parmer, EW-25562-14	1	2	98.00	196.00
84		Measuring Pipettes, 10.0ml, 12/cs (reusable), Cole-Parmer, EW-25562-16	1	2	115.00	230.00
85		Transfer Pipettes, 3ml, 500/pkg, Cole-Parmer, EW-06226-40	1	2	26.00	52.00
86		Transfer Pipettes, 5ml, 500/pkg, Cole-Parmer, EW-06226-60	1	2	25.00	50.00
87		Falcon Serological Pipettes, 2ml, 500/pkg, Cole-Parmer, EW-13000-11	1	2	85.00	170.00
88		Falcon Serological Pipettes, 5ml, 500/pkg, Cole-Parmer, EW-13000-25	1	2	66.00	132.00
89		Falcon Serological Pipettes, 10ml, 500/pkg, Cole-Parmer, EW-13000-35	1	2	59.00	118.00
90		PCR Tubes, 0.2ml, 1000/pkg, Cole-Parmer, EW-67103-90	1	3	70.00	210.00
91		PCR Tubes, 0.5ml, 1000/pkg, Cole-Parmer, EW-67104-60	1	3	58.00	174.00
92		Eppendorf Safe-Lock Microcentrifuge Tubes (1000/pkg, 1.5 ml), Sigma, T9661	1	3	48.00	144.00
93		Sterile Culture Tubes with two position PE caps, 6ml, 1000/cs, Cole-Parmer, U-06339-90	1	2	112.00	224.00
94		Corning graduated conical centrifuge tubes, 15 ml, 500/pkg, Corning, 430052	1	1	196.00	196.00
95		Corning graduated conical centrifuge tubes, 50 ml, 500/pkg, Corning, 430290	1	1	223.00	223.00
96		Corning cell culture flasks, 25cm2, 500/pkg, Corning, 430372	1	2	473.00	946.00
97		Test Tubes, 20ml, 576/pkg (reusable), Cole-Parmer, EW-34569-25	1	1	368.00	368.00
98		Tube Vacutainer EDTA CG, 2ml, 1000/cs, BD, BD364300	1	5	152.00	760.00
99		Tube PLH NOADD, 3ml, 1000/cs, BD, BD366703	1	5	139.00	695.00
100		Supor membrane bottle top filter unit (0.2 mkm, 10 each), Sigma, Z35,315-9	1	1	162.00	162.00
101		Test Tube Caps, h=13.5mm, 1000/box, Cole-Parmer, EW-34581-21	1	1	100.00	100.00
102		Test Tube Brashes, 12/pkg, Cole-Parmer, EW-84550-51	1	1	26.00	26.00
103		Parafilm M, 5cmx75cm, ROTH, H951.1	1	1	36.00	36.00

104		Nalgene Cryogenic Vials, 2.0ml, 500/pkg, Sigma, V5007	1	1	170.00	170.00
105		Flasks, 50ml, 12/pkg, Cole-Parmer, EW-34503-03	1	1	61.00	61.00
106		Flasks, 250ml, 12/pkg, Cole-Parmer, EW-34503-05	1	1	61.00	61.00
107		Flasks, 500ml, 12/pkg, Cole-Parmer, EW-34503-07	1	1	39.00	39.00
108		Flasks, 1000ml, 12/pkg, Cole-Parmer, EW-34503-08	1	1	62.00	62.00
109		Beakers, 30ml, 12/pkg, Cole-Parmer, EW-34502-03	1	1	49.00	49.00
110		Beakers, 50ml, 12/pkg, Cole-Parmer, EW-34502-04	1	1	49.00	49.00
111		Beakers, 150ml, 12/pkg, Cole-Parmer, EW-34502-06	1	1	49.00	49.00
112		Funnels, d=10, 6/pack, Cole-Parmer, EW-34563-04	1	1	98.00	98.00
113		Plastibrand wash bottles, LDPE, 500ml, 10/pkg, Sigma, Z32,962-2	1	1	57.00	57.00
114		Brand wash head for wash bottles, LDPE, 10/pkg, Sigma, Z32,965-7	1	1	14.00	14.00
115		Pipetor Tri-/Clamp-ette, blue, Sigma, P0614	1	1	49.00	49.00
116		Pipetor Tri-/Clamp-ette, red, Sigma, P0739	1	1	49.00	49.00
117		Pipetor Tri-/Clamp-ette, purple, Sigma, P0864	1	1	49.00	49.00
118		One well rack (5 each), Sigma, Z 70,848-8	1	2	27.00	54.00
119		Reversible 96 well rack (5 each), Sigma, R6151	1	1	108.00	108.00
120		Microcentrifuge tube rack, Nalgene, blue (0.5ml 96 tubes), Sigma, R1766	1	2	27.00	54.00
121		Watman paper 3MM Chr. (46x57, 100/pkg), Sigma, Z27,085-7	1	1	263.00	263.00
122		Watman paper 1 Chr. (46x57, 100/pkg), Sigma, Z27,082-2	1	1	176.00	176.0
123		Watman paper - #3 (100/pkg, d=5.5cm), Sigma, Z24,040-0	1	32	15.00	480.00
124		Blotting-Nylon 66 membranes, (type B, positive, roll), Sigma, 15356	1	2	297.00	594.00
125		Kodak X-Omat AR Film (8x10inch, 50/pkg), Sigma, F5763	1	1	378.00	378.00
126		Exposure Cassette Kodak BioMax (8x10 in film), Sigma, C4729	1	1	284.00	284.00
127		Kodak X-Omatic Regular Intensifying Screens, Sigma, Z356999	1	1	220.00	220.00
128		GBX developer/replenisher (1gal),Sigma, P7042	1	2	20.00	40.00
129		GBX fixer/replenisher (1gal), Sigma, P7167	1	2	18.00	36.00
130		Polaroid b/w films 667 (2x10/pak), ROTH, L130.1	1,5	10	34.00	340.00
131		Greiner tissue culture treated multiwell plates, V-bottom, 75/pkg, Sigma, M9561-75EA	1	2	115.00	230.00
132		Eppendorf 96 deepwell plates (1.2ml, 50/pkg), Eppendorf, 0030127.544	1	1	230.00	230.00
133		Eppendorf mat for 96 deepwell plate (1.2ml), Eppendorf, 0030127552	1	1	136.00	136.00
134		Gloves, small (100/pkg), Sigma, Z23,032-4	1	3	26.00	78.00
135		Gloves, medium (100/pkg), Sigma, Z23,031-6	1	3	27.00	81.00
136		Microscope slides, 10 gros./cs, VWR,48300-720	1	5	135.00	675.00
137		Coverslips, case of 10 OZ., ROTH, 0657.1	1	4	112.00	448.00
138		Immersion oil, 1L, Sigma, 56822	1	1	88.00	88.00
139		Silicon dioxide (Sand), 1kg, Sigma, 274739	1	1	32.00	32.00
140		Nalgene Vacuum Dessicator, Sigma, D2797	1	1	125.00	125.00
141		Brand Pursept-AF disinfectant, 2L, Sigma, Z637378	1	1	65.00	65.00
142		Inoculating loops (6/pkg), Cole-Parmer, EW-14-203-23	1	2	39.00	78.00
143		Disposable forceps, 100/pkg, Cole-Parmer, EW-06443-15	1	2	45.00	90.00
144		Sharpie permanent markers (10/box), Cole-Parmer, EW-09964-00	1	1	19.00	19.00
145		Nylon Organdy Fabric 45 inch mesh, white color, 1 yard, (supplier A&S Ltd.)	1	100	6.20	620.00
146		Cotton roll, medium, sterile, 1.5x0.357 inches, 2000/box, Henry Schein, 1002525TV	1	10	30.00	300.00
147		Dental Dam 6x6, green, medium, 36/box, Henry Schein, 5476730TV	1	6	10.00	60.00
148		Dehidrated sponges, 12/pkg, Henry Schein, 58540-047	1	10	25.00	250.00

149		Plastic tubs, 5.000mlx210mm, 25/cs., DUNN Labortechnik, JWH 5000P	1	4	81.00	324.00
150		Plastic tubes, 1.000mlx120mm, 100/cs., DUNN Labortechnik, JWH 1000P	1	2	115.00	230.00
151		Plastic tubes, 500mlx90mm, 25/cs., DUNN Labortechnik, JWH 0500P	1	2	88.00	176.00
152		Tygon Tubing-3/8x1/2x1/16, 50 feet (15m), Norton (Kleinfeld), AAX00027	1	2	101.00	202.00
153		Tygon Tubing-1/4x3/8x1/16, 50 feet (15m), Norton (Kleinfeld), AAX00017	1	2	74.00	148.00
154		Colored tape, blue, 1 inch wide, roll, Neolab, 2-6227	1	10	15.00	150.00
155		Colored tape, green, 1 inch wide, roll, Neolab, 2-6223	1	10	15.00	150.00
156		Colored tape, pink, 1 inch wide, roll, Neolab, 2-6224	1	10	15.00	150.00
157		Colored tape, red, 1 inch wide, roll, Neolab, 2-6225	1	10	15.00	150.00
158		Labelling dots, white, self adhesive, 1000/box, Neolab, 2-6252	1	2	19.00	38.00
159		Hydrometer/Thermometer with dual min-max memory, FisherSci, 3105861	1	10	70.20	702.00
160		Lactic acid, 1L, Sigma, 69775	1	3	45.00	135.00
161		Phenol (crystals), 1kg, Sigma, W322318	1	2	40.00	80.00
162		PVA mounting medium (PVA-DABCO), 100 ml, Sigma	1	2	110.00	220.00
163		Minuten pins, stainless, 0.15mm, 500/2pkg, Bioquip, 1207SA	1	10	12.20	122.00
164		Minuten pins, stainless, 0.20mm, 500/2pkg, Bioquip, 1207SB	1	5	12.00	60.00
165		Collection bag, double ring, fine mesh only, John Hock, 1.45	1	20	31.00	620.00
166		Collection bag, single ring, fine mesh, John Hock, 1.42	1	10	24.00	240.00
167		Insulin Syringes, 1cc, 500/cs, Tonus Ltd., (Lic. Nr.00044; 14 Khvamli Str., Tbilisi, Georgia)	1	26	55.00	1430.00
168		Luer-Lock Syringes, 5cc, 400/cs, Tonus Ltd., (Lic. Nr.00044; 14 Khvamli Str., Tbilisi, Georgia)	1	26	38.00	988.00
169		Syringes for bone marrow collection (autoclavable), 20cc, "Record", Ru (supplier A&S Ltd.)	1	50	2.00	100.00
170		Bone marrow biopsy needles - "Kasirski's needle", "Medicoinstrumental Factory", Moscow, Ru (supplier A&S Ltd.)	1	50	4.00	200.00
171		Ultra Fine Lancet, 2400/cs, BD, 325773	1	5	262.00	1310.00
172		Protection glasses Labotect, 325120	1	1	25.00	25.00
173		Syringes 1cc, Palmer Cap-Chur Equipment, 3000	1	150	8.40	1260.00
174		Syringes 2cc, Palmer Cap-Chur Equipment, 3300	1	150	8.60	1290.00
175		Syringes 3cc, Palmer Cap-Chur Equipment, 3600	1	150	8.80	1320.00
176		Cap-Chur charges, 50/jar, Palmer Cap-Chur Equipment, 2361	1	44	23.00	1012.00
177		CO_2 gaspaks, 12/box, Palmer Cap-Chur Equipment, 2371	1	18	11.50	207.00
178		Rubber Plunger, 24/pkg, Palmer Cap-Chur Equipment, 2443	1	3	30.00	90.00
179		ACES 40" Pole Syringe, ACES, KPS-03	1	4	50.00	200.00
180		EJAY ID Bands, 500/pkg, ACES, EJR-10	1	1	34.00	34.00
181		EJAY ID Bands, 500/pkg, ACES, EJR-15	1	2	36.00	72.00
182		EJAY ID Bands, 500/pkg, ACES, EJR-20	1	1	37.00	37.00
183		Pro-Guard Softie Dog Muzzle, Morrco Pet Supply, Proguard	1	5	16.00	80.00
184		Work Gloves, Midwestcapture, GL-41	1	4	10.00	40.00
185		Mouth Aspirator with HEPA filter - Model 612, John Hock, 612	1	20	30.00	600.00
186		Sealed Gelled-Electrolyte Battery, 6 Volt, 10 Amp Hours, John Hock, 2.30	1	30	28.00	840.00
					Subtotal:	**68462.00**
					Estimated TOTAL COST:	**68462.00**

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10.4. Other Direct Costs Summary

TABLE 4

OTHER DIRECT COSTS SUMMARY

OTHER DIRECT COSTS SUMMARY

for Project Agreement #G-1081

To be provided in kind [X]
To be purchased by recipient [ ]

Detailed breakdown of Other Directs Costs to include planned activities under items 5.1, 5.2, 5.3, 5.4, 5.5 from Table 1 of the Project Agreement

Item No.		DESCRIPTION OF ITEM	Date needed (quarter)	Qty	Unit cost (USD)	Amount (USD)
Leading Institution: NCDC						
1	5.4	Logistics/Customs	1	1	1560.00	1560.00
2	5.4	Logistics/Customs	1	1	1500.00	1500.00
3	5.4	Logistics/Customs	2	2	1000.00	2000.00
4	5.4	Logistics/Customs	5	1	300.00	300.00
5	5.4	Logistics/Customs	5	1	150.00	150.00
6	5.4	Logistics/Customs	5	1	200.00	200.00
7	5.4	Logistics/Customs	5	1	750.00	750.00
8	5.4	Logistics/Customs	6	1	100.00	100.00
9	5.4	Logistics/Customs	6	1	100.00	100.00
10	5.4	Logistics/Customs	9	2	200.00	400.00
					Subtotal:	**7060.00**
					Estimated TOTAL COST:	**7060.00**

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TABLE 4-1

OTHER DIRECT COSTS SUMMARY

OTHER DIRECT COSTS SUMMARY

for Project Agreement #G-1081

To be provided in kind [ ]
To be purchased by recipient [X]

Detailed breakdown of Other Directs Costs to include planned activities under items 5.1, 5.2, 5.3, 5.4, 5.5 from Table 1 of the Project Agreement

Item No.		DESCRIPTION OF ITEM	Date needed (quarter)	Qty	Unit cost (USD)	Amount (USD)
Leading Institution: NCDC						
1	5.2	Communications	1-12	36	42.00	1512.00
2	5.3	Subcontracts	1-12	24	120.00	2880.00
3	5.5	Booklet design	1	1	200.00	200.00
4	5.5	Booklets printing	1,2	10000	0.15	1500.00
5	5.5	Poster design	1	1	250.00	250.00
6	5.5	Posters printing	1,2	3000	0.35	1050.00
7	5.5	Questionnaires printing	1-3	4500	0.15	675.00
8	5.5	Other	1-12	12	150.00	1800.00
					Subtotal:	**9867.00**
					Estimated TOTAL COST:	**9867.00**

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ANNEX II
General Conditions

Contents:

Annex II General Conditions

Part A - Implementation of the Work

Article 1 - General Provisions

1.1 The Recipient shall make best efforts to achieve the objectives of the Project and shall comply with all laws of the Republic of Georgia applicable to the Project. If in the course of project implementation deliverables are identified that may qualify under export control restrictions, the Recipient takes responsibility for timely obtaining the corresponding export licenses, and operating in compliance with all Russian, CIS and International laws and regulations.

1.2 The Recipient shall, in particular, comply with all applicable laws and regulations related to safety.

1.3 The Recipient shall notify the Center's Project representative and the Partner without delay of:

(a) any event or circumstance which may materially affect the Project, and
(b) any proposal for significant changes of key personnel during the Project.

Article 2 - Subcontracting

2.1 Subcontracting shall require the advance written approval of the Center, with the concurrence of the Partner. However, approval shall not normally be given for subcontracting in any State that is not a Party to the ISTC Agreement unless the Center determines in writing that such subcontracting is essential for the Project.

2.2 The Recipient shall impose on a subcontractor the same obligations as apply to itself with respect to any rights of the Center or the Partner concerning the Project.

2.3 The provisions of Article 2.1 of this Annex shall not apply to Sub-Agreements pursuant to Article 3 of the Agreement or to orders for materials, equipment, and services which are incidental to or intended to facilitate the execution of the Agreement and placed in the normal course of business in accordance with the internal procedures and rules of the Recipient.

Article 3 - Monitoring of the Work

3.1 The Center shall:

(a) Have access to portions of facilities where the Project is being carried out and to all equipment, documentation, information, data systems, materials, supplies, personnel and services which concern the Project for monitoring the progress of the Project as described in Annex I;

(b) Be provided with technical and cost information concerning the management and progress of the Project requested at any time; and

(c) Give the Recipient not less than 20 days advance notice of any intended on-site financial auditing or technical monitoring of the Project.

3.2 The Recipient has the right to protect those portions of facilities that are not related to the Project.

3.3 After completion or termination of the Project, the Recipient may utilize the facility or portion of the facility previously used for the Project for other work. However, all documentation and records including those associated with equipment, data systems, materials, supplies and services utilized for the Project must be maintained and available for review by the Center for up to two years following the Project's completion or termination.

3.4 The Recipient shall, if requested by the Center, participate and assist in meetings to review or evaluate the Project during the lifetime of the Project.

Article 4 - Reports

4.1 The Recipient shall submit the following reports, in a suitable quality to enable direct reproduction, to the Center and the Partner for approval:

(a) A final report, in English and Russian, covering all the work, the objectives, the results and the conclusions, including a suitable summary of all these aspects; and

(b) Reports, as mutually agreed, prepared in a suitable form for publication and satisfactory to the Partner and the Center.

4.2 The Recipient shall submit any additional reports or any other deliverables specified in the Agreement.

4.3 The Recipient should clearly identify any reports or portions of reports that contain invention or business confidential information as defined in Part E of this Annex. The final report shall include a statement that all inventions Made during the performance of work under the Agreement have been reported to the Center and to the Partner, or if no inventions were Made, a statement to that effect. The Recipient also may include a suitable disclaimer in any report against possible claims by third parties.

Article 5 - Completion or Expiration of the Agreement

5.1 The Agreement shall be deemed to be completed on the approval by the Center and the Partner of the last deliverable required or last payment by the Center, whichever shall be the later.

5.2 Subject and without prejudice to the provisions in Part D of this Annex, the Recipient shall be deemed to have discharged its obligations with respect to the performance of the work after the approval of all the reports and any other deliverables required by the Agreement.

Part B - Payments
Article 6 - Payments by the Center to the Recipient

Payments of allowable costs other than the Center's in-kind contributions, the Center's grant payments to Individual Participants and overhead payments shall be made in accordance with the following principles.

6.1 Cost statements shall be expressed in US dollars unless otherwise specified in the Agreement. All payments by the Center shall be made in that currency unless otherwise agreed.

6.2 The financial contribution by the Partner through the Center shall be paid in installments as specified in Article 5 of the Agreement.

6.3 If the Center or the Partner considers that the work has not effectively been commenced within three months of the payment of the first advance, the Center may require the reimbursement of the advance together with any interest earned on the advance. Any reimbursements will be returned to the Partner account.

6.4 If on completion, cessation, or termination of the work, the payments made by the Center exceed the actual allowable costs, the Recipient shall promptly reimburse the difference to the Center. Interest may be added to this amount at the prevailing market rate as determined by the Center one month after the reimbursement date specified by the Center. Any reimbursements will be returned to the Partner account.

6.5 Subject to Article 12 of this Annex, periodic payments made against cost statements shall be considered as advances until acceptance of the appropriate deliverables, in accordance with Annex I, or, if no deliverables are specified, until acceptance of the final report.

Part C - Allowable Costs
Article 7 - Accounting Principles, Allowable Costs, and Transfer of Costs

7.1 The original estimates of expenditures set forth in Annex I may be adjusted by the Recipient between categories without the prior approval of the Center, except for reductions in personnel costs and increases in travel costs, and provided that the transfers do not fundamentally affect the scope or content of the Project.

7.2 The Recipient shall ensure that no unnecessary cost or unnecessarily high or extravagant cost is charged to the Agreement.

Article 8 - Direct Costs

8.1 Personnel

8.1.1 Personnel costs shall be separated into four categories as described in Annex I and reflected in the reporting form in Annex III. Even though some or all of these costs may be reimbursed by the Center through direct grant payments to the Individual Participants, the Recipient is responsible for certifying the time devoted to the Project by the Individual Participants and for maintaining necessary documentation to support such certification.

8.1.2 Personnel costs shall be charged to reflect the actual eight-hour days, or one-half days when appropriate, worked by personnel assigned by the Recipient to the Project in accordance with Annex I. Work periods of less than four hours may not be charged.

8.1.3 Personnel costs for a specific period of time may not be charged to this Project if reimbursement (except regular employment salary) is being received from other sources for the same period of time.

8.1.4 The Project Manager may increase or decrease the time commitments of personnel by up to 10 percent during one year of any individual without approval of the Center, but may not change the daily rate without approval by the Center. The Project Manager may request more significant changes in the personnel commitments, including changes in the names of the personnel, at the beginning of each quarter with a brief explanation of the reasons for the changes. In unusual situations, the Project Manager may request changes during the quarter. The Center, in consultation with the Partner, will respond promptly to such requests. Changes in scientific personnel must provide for the new participants to have technical credentials and weapons experience comparable to those of the personnel they replace.

8.1.5 The Center will not reimburse personnel costs associated with holidays, annual vacations, overtime, or sick leave. Such additional costs, if any, are the responsibility of the Recipient.

8.1.6 The Project Manager shall ensure that the scheduling of annual leave by the Individual Participants does not interfere with accomplishment of the Work Plan in Annex I.

8.1.7 The Recipient is responsible for any medical expenses or compensation claims for injuries or other losses for personnel working on the Project which are directly or indirectly related to the Project.

8.1.8 Individual weekly records of time devoted to the Project must be signed by all personnel assigned to the Project, and all records must be certified at least monthly by the Project Manager and for the Project Manager by another appropriate senior employee of the Recipient.

8.2 Equipment

8.2.1 Equipment shall be categorized as indicated in the reporting form in Annex III.

8.2.2 The cost of equipment used in the Project which is purchased, fabricated, or leased after the Operative Commencement Date may be charged as a direct cost. The total leasing cost of any piece of equipment shall not exceed the cost which would have been allowable for its purchase.

8.2.3 Notwithstanding Article 4.5.1 of the Agreement, the Center will retain the title to all the equipment provided to or procured by the Recipient using Center funds regardless of the acquisition per item cost of the equipment. The final decision of possible transfer of the title shall be taken by the Center, in consultation with the Financing Party, by the time of completion, termination or cessation of the Project taking into account the specific legal, institutional and other factors in effect in the state of the Recipient at that time.

8.3 Materials

The costs of required materials shall be allowable costs. They shall be categorized as raw materials, laboratory supplies, safety devices and protective gear and other as indicated on the reporting form in Annex III.

8.4 Other Direct Costs

8.4.1 Other direct costs shall be categorized as indicated in the reporting form in Annex III.

8.4.2 Costs incurred by the Recipient in using its internal resources for performance of the Agreement such as costs associated with (a) testing facilities, (b) computer services, (c) special test equipment, (d) dedicated security services, and (e) dedicated accounting services, but excluding items covered by Article 9 of Annex II, may be charged as direct costs through valid cost allocation formulas approved by the Center to the extent such costs contribute to the Project, provided such facilities and services are open to access for monitoring and auditing in accordance with Article 9 of the Agreement. If costs incurred by the Recipient are not charged as direct costs, they may be presented as in-kind contributions of the Recipient.

8.5 Travel and Per Diem for the Recipient

Travel and per diem within the CIS shall be charged in accordance with the internal rules of the Recipient which are subject to approval by the Center. International travel shall be provided by the Center in accordance with Article 4 of the Agreement.

8.6 Sub-Agreements and Subcontracts

8.6.1 Subject to Article 2 of this Annex, costs of subcontracts shall be allowable costs and shall be included as discrete entries in the appropriate categories on the reporting form of Annex III. If the subcontractor is a scientific institution engaged in a sub-agreement pursuant to Article 3 of the Agreement, costs are allowable only to the extent that they would be allowable if incurred directly under the Agreement. In selecting a subcontractor other than a scientific institution pursuant to Article 3 of the Agreement, the Recipient shall compare prices and quality of several subcontractors and choose the most cost-effective offer. For any subcontract costing more than the equivalent of $25,000, the Recipient shall organize a bidding process. For any subcontract costing between $10,000 and $25,000 (equivalent) written quotations shall be obtained from three sources to the extent possible.

8.6.2 Should the Recipient enter into a sub-agreement with a scientific institution pursuant to Article 3 of the Agreement, the reporting form in Annex III shall include the costs incurred pursuant to the sub-agreement which shall be supported by detailed information.

Article 9 - Overhead

A fixed payment may be charged with respect to overhead which covers items such as general administration, institutional management, depreciation of buildings and general equipment, maintenance of building and grounds, telephones, heating, lighting, electricity for the buildings and general staff training.

The payment shall not exceed 10% of the direct Project costs, excluding equipment, travel and subsistence.

Since the overhead will be retained by the Center until acceptance of the final report, the Recipient need not include this item on the reporting form in Annex III.

Article 10 - Costs Not Allowed

Allowable costs shall not include, among others:

- any profit;
- any contributions to pension, medical, or other social funds;
- any provisions for possible future losses or liabilities;
- any taxes, including profit tax, value added tax, personal income tax, and local taxes, as well as any other tariffs, dues, custom duties, import duties, fees, or other imposed taxes or similar charges;
- any costs allocatable to other projects.

The Center will determine the use of any interest earned from funds provided by the Center or return on investment of such funds. Such interest or return on investment must be reported to the Center.

Part D - Justification of Costs and Auditing
Article 11 - Books of Account and Documentation

The Recipient shall maintain, in accordance with the accounting practices set forth in the Agreement, proper books of account and appropriate documentation, such as invoices and time sheets to support and justify the costs reported. These shall be made available for audits by the Center during the period of the Project and for a period of up to two years following the Project's completion or termination.

Article 12 - Auditing

12.1 Cost statements are subject to verification even after the Center has reimbursed costs. The Center has the right pursuant to the ISTC Agreement and ISTC Statute to carry out on-site auditing of all activities of the Project. The Recipient will be given not less than 20 days notice of any intended audit. For the purposes of the audit, the Recipient shall make accessible all portions of facilities, equipment, documentation, information, data systems, materials, supplies, personnel and services related to the Project.

12.2 The Recipient has the right to protect those portions of facilities that are not related to the Project.

12.3 The Recipient shall maintain all documentation and records including those associated with equipment, data systems, materials, supplies and services utilized for the Project and shall make such documents, records and, to the extent possible, personnel available for auditing for a period of up to two years following the Project's completion or termination.

12.4 The Center shall have the right to select Courts of Auditors or other organizations or individuals to carry out audits of the Project; they shall be entitled to the same rights, should they choose to exercise them, as the Center with respect to access to, and verification of, any document under the Agreement for the purpose of any audit.

Part E - Information and Intellectual Property
Article 13 - Definitions

13.1 "Intellectual Property" includes inventions, patents, copyrights and other forms of protection provided by statutes, such as, industrial designs, design patents, mask works, and trademarks, and has the meaning defined in Article 2 of the Convention Establishing the World Intellectual Property Organization, done in Stockholm on July 14, 1967, which states: "Intellectual Property shall include the rights relating to:

- literary, artistic and scientific works,
- performances of performing artists, phonograms, and broadcasts,
- inventions in all fields of human endeavor,
- scientific discoveries,
- industrial designs,
- trademarks, service marks, and commercial names and designations,
- protection against unfair competition,

- and all other rights resulting from intellectual activity in the industrial, scientific, literary or artistic fields."

13.2 "Information" includes technical data and computer software and means recorded data of any kind of a scientific or technical nature, regardless of the form or method of recording, and capable of being read by a human being or processed by a machine.

13.3 "Foreground Results" means Foreground Information and Foreground Intellectual Property.

13.4 "Foreground Information" means Information, including all kinds of results, generated in the execution of this Agreement.

13.5 "Foreground Intellectual Property" means rights in Intellectual Property generated in the execution of this Agreement by the Recipient or any person employed or engaged by the Recipient.

13.6 "Background Results" means Background Information and Background Intellectual Property.

13.7 "Background Information" means Information, excluding Foreground Information, owned or controlled by either the Recipient or Partner in the same or related fields as the research under this Agreement and generated outside this Agreement.

13.8 "Background Intellectual Property" means rights in Intellectual Property, excluding Foreground Intellectual Property, owned or controlled by either the Recipient or Partner in the same or related fields as the research executed under this Agreement and originating outside this Agreement.

13.9 "Business Confidential Information" is also known as trade secret information and means technical, commercial or financial information, which:
Has been held in confidence by its owner;
Is not generally known or available from other sources;
Has not been made available by its owner to other parties without an obligation concerning its confidentiality;
Has not been independently developed by the receiving party; and
Is not available to the receiving party without obligations concerning confidentiality.

13.10 "Invention Information" is Intellectual Property which is to be protected by a patent and on which a patent has not been filed.

13.11 "Made," when used in relation to any invention, means the conception or first actual reduction to practice of such invention.

13.12 "Unlimited rights" means the right to use, modify, reproduce, perform, display, release, or disclose Information in whole or in part, in any manner, and for any purpose whatsoever, and to have or authorize others to do so.

Article 14 - Promotion of Technology and Project Results

Confidentiality

14.1 Subject to Article 4.1(c), all reports or portions of reports properly marked as Invention Information or Business Confidential Information by the Recipient in consultation with the Partner shall be protected from public dissemination unless otherwise agreed by the Recipient and the Partner. Invention Information is treated as Business Confidential Information until a patent application has been obtained unless such information so disclosed is or becomes legitimately available to the receiving Signatory Party through other means or sources without any covenant as regards its confidentiality. Nevertheless, Business Confidential Information may be disclosed if the disclosure is required by law, regulation, or court order.

14.2 Subject to any obligations under this Agreement and in accordance with applicable laws and regulations, the Signatory Parties agree to keep confidential any Invention Information or Business Confidential Information communicated to them by other Signatory Parties or third parties in relation to the execution of this Agreement, unless such information so disclosed is or becomes legitimately available to the receiving Signatory Party through other means or sources without any covenant as regards its confidentiality. Nevertheless, Business Confidential Information may be disclosed if the disclosure is required by law, regulation, or court order.

Technology Promotion

14.3 The ISTC shall be entitled to publish general information on this Agreement including the identities of the Recipient and Partner, the title and objective of the Agreement, its estimated costs and duration, and the names of managers and laboratories where the research is being carried out.

14.4 Each Signatory Party agrees to submit to each other Signatory Party for review and approval a copy of any proposed publication of Foreground Information at least thirty days before such publication.

14.5 Any public communication or publication concerning this Project will acknowledge the Recipient, the Partner and the cooperative support of the ISTC.

14.6 Subject to the restrictions of Article 14.1, each Party to the ISTC Agreement (hereinafter referred to as the "**ISTC Party**") and the ISTC have a non-exclusive, irrevocable, royalty-free license with the right to sub-license in all countries to translate, reproduce and publicly distribute scientific and technical journal articles, reports, and books directly arising under this Agreement. All publicly distributed copies of a copyrighted work arising from cooperation under this Agreement shall indicate the names of the authors of the work, unless an author explicitly declines to be named.

Article 15 – Ownership of Intellectual Property and Foreground Information

15.1 In accordance with the ISTC Statute, except for inventions created by United States Government employees, all rights worldwide to Intellectual Property arising under this Agreement, including patent protection for industrial property, belong to the Recipient (or its designee), which has the responsibility for providing adequate protection of such Intellectual Property. The Recipient and the Partner have agreed to protect and allocate such Intellectual Property among each other as specified in Article 16 below. Rights to inventions made by United States Government employees or made in Partner's laboratory shall be determined by the United States.

15.2 All rights worldwide to Foreground Information arising under this Agreement belong to the Recipient (or its designee). The United States Government, as represented by Partner, is granted a non-exclusive, irrevocable, royalty-free, worldwide license of unlimited rights in Foreground Information.

Article 16 - Protection and Exploitation
16.1 Intellectual Property Rights (IPR) Allocation

(i) The work conducted under this project is expected to generate new intellectual property by the Recipient and its Partner
(ii) The protection and allocation of intellectual property created or furnished in the course of the cooperative research activities pursuant to this Agreement shall be provided in accordance with the Articles 16.2, 16.3, 16.4, 16.5, 16.6, 16.7, 16.8, 16.9 of the Annex II.
(iii) Any publications or presentations of information developed by the project participants shall acknowledge their funding support and shall be cleared by the institutions involved according with the existing procedures. Joint work is expected to result in joint authorship of publications.
(iv) The development of any new commercial products and commercialization of results are not expected to be the issue during the term of the project
(v) However if this proves otherwise, the Recipient and its Partner agree to notify one another as well as other Parties of the Agreement in a timely fashion of any invention or copyrighted works arising under this Project and to seek protection for such intellectual property in a timely fashion.
(vi) The Recipient and the Partner shall be responsible for the maintenance, protection and preservation of all intellectual property during the term of the project

16.2 Ownership and Non-exclusive License: With the exception of inventions made by employees of the United States Government, the Recipient owns worldwide rights to Intellectual Property arising under this Agreement. The United States Government as represented by the Partner shall determine the rights in inventions made by United States Government employees or made in U.S. Government facilities. The United States Government, as represented by partner, is granted in all Intellectual Property arising under this Agreement a non-exclusive, irrevocable, royalty-free, worldwide (except for the territory of the United States) license to practice or have practiced for or on behalf of the United States. Upon the request of the Partner (or its designee), the Recipient entity (or its designee) shall enter into negotiation with United States commercial entities for licenses for commercial purposes on fair and reasonable terms in territories other than the United States in all Intellectual Property arising under this Agreement.

16.3 Commercialization in the United States: Upon request by Partner, the Recipient shall assign to the Government of the United States as represented by Partner, subject to a royalty-free, irrevocable non-exclusive license to the recipient, the entire right, title, and interest in any Intellectual Property in the United States, including inventions, patents on inventions, and copyrights arising under the Agreement. The Government of the United States will obtain and pay for all costs of obtaining patent protection in the United States on those inventions that the Recipient and Partner mutually agree to obtain patent protection in the United States (See Article 16.6). All uses of the Intellectual Property by or for the Government of the United States are royalty free. When the Government of the United States as represented by Partner or Partner's designee, negotiates and executes a license for commercial purposes to use Intellectual Property within the territory of the United States, which are purposes other than those by or for the Government, compensation will be sought for all uses of the Intellectual Property.

16.4 Compensation for inventors: In accordance with the policies of the Partner, which provide that the inventive entity shall receive at least 15% of royalties received, the inventors will receive a portion of the royalty income. The remaining royalties will be applied to cover or offset expenses incurred in obtaining and maintaining patent protection; and any remaining royalty income, after paying patent expenses, will be shared equally between the Recipient and Partner. However, the inventor, or inventors as a group, will always receive at least 15% of the total royalties received each year in accordance with the policies of the Partner.

16.5 Disclosure of inventions within two months: A written disclosure of invention will be provided by the Recipient (or its designee) to the Partner within two months of the date on which the invention is Made. See Article 17.2

16.6 Election to file patent applications within six months: The Recipient will notify Partner within six months of reporting an invention of each territory, except for the territory of the United States, in which the Recipient elects to protect the invention through patenting. In the territory of the United States, election to file will be by mutual agreement of the Recipient and Partner, and if the parties are unable to agree within eight months of reporting an invention and the Partner has not requested assignment under 16.3, either the Recipient or Partner may elect, by notifying the other party, to obtain patent protection in the United States and the party electing to file will pay all patent costs and will not share royalties with the Party not electing to file. If the Recipient files for a patent in the United States, the Government of the United States, as represented by Partner, shall have a non-exclusive, irrevocable, royalty-free license to practice or have practiced for or on behalf of the United States. See Articles 16.3 for patent costs and 17.3.

16.7 Filing of patent applications: The Recipient will file the first patent application within twelve months of reporting the invention. Partner has right to file patent applications in the countries in which the Recipient does not elect to file. If the Recipient does not elect to file within eight months of the date on which the invention is Made, the Partner may file applications in all countries in which the Recipient does not elect to file, and the Recipient will assign title to the invention to the Partner in those countries in which the Partner has filed. The Recipient will retain a non-exclusive irrevocable, royalty free license in the territory where the Partner has filed. See Article 17.3

16.8 Exploitation of Results: The Technology Implementation Plan required by Article 8.2 of the Project Agreement shall contain a listing of all inventions Made under the Agreement, the status of pending patent

applications, or patent numbers, licenses granted and in negotiation, and relate the commercial results of the research performed under the Agreement with the anticipated commercial results and intellectual property rights described in the proposal submitted for the Agreement.

16.9 The Recipient will grant to the United States Government, as represented by Partner, under reasonable terms and conditions the right to use by or for the Government Background Results owned by the Recipient which are necessary for the Partner to exploit Foreground Results, provided that the Recipient is free to disclose such Background Results, that no major business interests of the Recipient oppose the granting of such right, that in making this opposition such interests are not abusively restricting the exploitation of such right and that granting such right is not restricted by the law or obligations to a third party. The Recipient will notify the Partner, with factual statements in the next monthly technical report, of all situations where: the Recipient is not free to disclose such Background Results; or a major business interest opposes the granting of such right to such Background Results; or the disclosure of such Background Results is restricted by law or obligations to a third party.

Article 17 - Reporting of Inventions

17.1 The Recipient will disclose to the Partner and the ISTC in an ISTC-approved form every invention Made under this Agreement within two (2) months of the date on which such invention is Made. These disclosures must be in sufficiently complete technical detail to convey a clear understanding, to the extent known at the time of the disclosure, of the nature, purpose and operation of the invention.

17.2 The Recipient and the Partner will notify the ISTC of each territory in which each (or their designees) decides to protect inventions through patenting within six (6) months of the reporting of such inventions in accordance with Article 17.1 above.

17.3 The Recipient and the Partner will file patent applications in each territory in which each (or its designee) decides in accordance with Article 17.2 above to protect each invention through patenting. The first patent application will be filed in the territory where the invention was Made within twelve (12) months of reporting the invention in accordance with Article 17.1 above. The remaining patent applications will be filed in the other territories within respective time periods to ensure that the priority date of the first patent application is obtained for these later filed applications. The Recipient and the Partner will provide each other and the ISTC with copies of all patent applications each (or its designee) files.

Article 18 - Background Results

The Recipient and the Partner have identified and agreed that the following Background Results may be used in the performance of work under this Agreement and may be needed to practice any Foreground Results of this Agreement:

Recipient's Background Results: *none* .
Partner's Background Results: *none*.

Recipient and Partner represent that the above-identified Background Results are available for licensing as of the effective date of this Agreement.

Article 19 - Conflicting Agreements, Laws and Regulations

19.1 Recipient certifies that it has not and will not enter into any agreement with a third party that grants to the third party rights to Foreground Results that may affect the exploitation or commercialization of Foreground Results received by the Partner under this Agreement.

19.2 Recipient shall notify the Partner and the ISTC of any restrictions by government laws or regulations which may materially and adversely affect the rights necessary for the performance of the work or the exploitation and commercialization of Foreground Results.

ANNEX III
Formats for Progress and Cost Reports

1. Format for Technical Reports

Quarterly reports shall specify the progress, any actual or proposed deviations and modifications to the Work Plan in Annex I, and the results obtained. The reports shall contain sufficient information to enable assessment of the progress and cooperation within the Project. The details of the Annual Report shall be agreed upon at an appropriate time by the Recipient and the Center's Project representative. A suggested format for quarterly reports is as follows:

I. Summary of Technical Progress (By task in the Work Plan)
II. Milestones Completed
III. Summary of Personnel Commitments
IV. Major Equipment Acquired
V. Description of Significant Travel
VI. Current Technical Status (on schedule, behind schedule, ahead of schedule)
VII. Delays, Problems, Suggestions

The quarterly report should be between three and five pages (single space).

2. Financial Forms

(The templates for reports are to be provided separately by the Center.)

3. Submission Dates for Technical and Financial Reports:

Technical and Financial reports are due two weeks after the end of each fiscal year quarter:

January 15
April 15
July 15
October 15

Additional time (two weeks) shall be granted for reconciliation (adjustments) of end-of-year balances.

ANNEX IV
DISCLAIMER

It is understood and agreed to by the Recipient of this ISTC project that:

The project funding commitment of the ISTC is subject to and limited by the funds which are actually available by the ISTC Financing Party(ies) for this project;

The funding for each project comes from ISTC Financing Parties and/or Partners who might make their ISTC financial contribution in whichever currency considered appropriate;

As a matter of practice, the ISTC at present signs all project agreements in a single currency, the US dollar;

The project support given to this project by the ISTC Financing Party(ies) and/or Partners of the ISTC may be affected by causes, including currency fluctuation, which may require adjustments in the project budget.

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ADDENDUM #7
TO
PARTNER PROJECT AGREEMENT #G-1081p

The International Science and Technology Center, Moscow, Russia (the "Center"), the National Institute for Disease Control and Medical Statistics, Tbilisi, Georgia (the "Recipient"), and the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH), Bethesda, MD, USA (the "Partner"), regarding the implementation of Project Agreement #G-1081p, have agreed upon the following:

1. The period of the project implementation shall be extended by 21 months until March 31, 2013 taking into account that in the period since July 01, 2011 until March 31, 2012 no project activities were carried out.

2. The previously planned funding amount for Project Agreement #G-1081p was US$ 442,009. Funding is being increased by US$ 50,000 for a revised funding total of US$ 492,009 to cover the work specified in Annex I – Revised Work Plan attached hereto.

3. The Recipient shall submit to the Center the additional quarterly and annual reports, and, after completion of the Project #G-1081p, the final report together with the consolidated cost statement, covering the additional period of the project execution.

4. The Center's in-kind contributions to the Recipient for International Travel will not to exceed US$ 37,647 under the conditions set forth in Article 4.5.4 of the Project Agreement.

5. All other terms and conditions specified in Project Agreement #G-1081p remain in effect.

Prepared in Moscow in the English language.

For the Center

Adriaan van der Meer
Executive Director

Date:

31 May 2012

For the Recipient

Dr. Nata Avaliani
Director

Date:

20.06.2012

For the Partner

William Rosa
International Program Coordinator

Date:

1 Jun 2012

I S T C

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ADDENDUM #8
TO
PARTNER PROJECT AGREEMENT #G-1081p

The International Science and Technology Center, Moscow, Russia (the "Center"), the National Institute for Disease Control and Public Health, Tbilisi, Georgia (the "Recipient"), and the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH), Bethesda, MD, USA (the "Partner"), regarding the implementation of Project Agreement #G-1081p, have agreed upon the following:

1. The period of the project implementation shall be extended by 12 months until March 31, 2014.
2. The previously planned funding amount for Project Agreement #G-1081p was US$ 492,009. Funding is being increased by US$ 70,000 for a revised funding total of US$ 562,009 to cover the work specified in Annex I – Revised Work Plan attached hereto.
3. The Recipient shall submit to the Center the additional quarterly and annual reports, and, after completion of the Project #G-1081p, the final report together with the consolidated cost statement, covering the additional period of the project execution.
4. The Center's in-kind contributions to the Recipient for International Travel will not to exceed US$ 42,434 under the conditions set forth in Article 4.5.4 of the Project Agreement.
5. The retention to be paid by the Center under the conditions set forth in Article 5.1 of the Project Agreement is US$ 15,000.
6. All other terms and conditions specified in Project Agreement #G-1081p remain in effect.

Prepared in Moscow in the English language.

For the Center	**For the Recipient**	**For the Partner**
Leo Owsiacki	Dr. Amiran Gamkrelidze	William Rosa
Executive Director	General Director	International Program Coordinator
Date: June 5/13	Date: 13.06.13	Date: 24 June 2013

I S T C

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ADDENDUM #9
TO
PARTNER PROJECT AGREEMENT #G-1081p

The International Science and Technology Center, Moscow, Russia (the "Center"), the National Institute for Disease Control and Public Health, Tbilisi, Georgia (the "Recipient"), and the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH), Bethesda, MD, USA (the "Partner"), regarding the implementation of Project Agreement #G-1081p, have agreed upon the following:

1. The period of the project implementation shall be extended by 9 months until December 31, 2014.
2. The Recipient shall submit to the Center additional quarterly and annual reports, and after completion of the Project, the final report together with the consolidated cost statement covering the additional period of the project execution.
3. All other terms and conditions of the Project Agreement #G-1081p, not modified by this Addendum, remain unchanged.

Prepared in Moscow in the English language.

For the Center	**For the Recipient**	**For the Partner**
David Cleave Acting Executive Director	Dr. Amiran Gamkrelidze General Director	William Rosa International Program Coordinator
Date: 23/05/14	Date:	Date: 16/06/14