

PD-ABD-642  
ISA 73294

UNCLASSIFIED

UNITED STATES INTERNATIONAL DEVELOPMENT COOPERATION AGENCY  
AGENCY FOR INTERNATIONAL DEVELOPMENT  
Washington, D. C. 20523

LAC REGIONAL

PROJECT PAPER

HEALTH AND NUTRITION TECHNICAL  
SERVICES SUPPORT  
AMENDMENT NUMBER 3

AID/LAC/P-678  
(CR-462)

PROJECT NUMBER: 598-0657

UNCLASSIFIED

<b>AGENCY FOR INTERNATIONAL DEVELOPMENT</b> <b>PROJECT DATA SHEET</b>		<b>1. TRANSACTION CODE</b> <input type="checkbox"/> A = Add <input checked="" type="checkbox"/> C = Change <input type="checkbox"/> D = Delete	<b>Amendment Number</b> 3	<b>DOCUMENT CODE</b> 3
<b>2. COUNTRY/ENTITY</b> LAC Regional		<b>3. PROJECT NUMBER</b> 598-0657		
<b>4. BUREAU/OFFICE</b> LAC/DR/HPN <input type="checkbox"/> 05		<b>5. PROJECT TITLE (maximum 40 characters)</b> Health and Nutrition Technical Services Support		
<b>6. PROJECT ASSISTANCE COMPLETION DATE (PACD)</b> MM DD YY 09 30 94		<b>7. ESTIMATED DATE OF OBLIGATION</b> (Under B' below, enter 1, 2, 3 or 4) A. Initial FY <input type="checkbox"/> 89 B. Quarter <input checked="" type="checkbox"/> 4 C. Final FY <input type="checkbox"/> 92		

**8. COSTS (\$000 OR EQUIVALENT \$1 = )**

A. FUNDING SOURCE	FIRST FY			LIFE OF PROJECT		
	B. FX	C. L/C	D. TOTAL	E. FX	F. L/C	G. TOTAL
AID Appropriated Total						
(Grant)	1,639		1,639	22,050		22,050
(Loan)						
Other U.S.						
1. Mission Buy-ins (Nonadd)				13,300		13,300
2.						
Host Country						
Other Donor(s)						
<b>TOTALS</b>	<b>1,639</b>		<b>1,639</b>	<b>22,050</b>		<b>22,050</b>

**9. SCHEDULE OF AID FUNDING (\$000)**

A. APPROPRIATION	B. PRIMARY PURPOSE CODE	C. PRIMARY TECH CODE		D. OBLIGATION TO DATE		E. AMOUNT APPROVED THIS ACTION		F. LIFE OF PROJECT	
		1 Grant	2 Loan	1 Grant	2 Loan	1 Grant	2 Loan	1 Grant	2 Loan
(1)H	590	500		3,873		251		8,941	
(2)CS	590	500		5,849		99		10,459	
(3)AIDS	590	500		100				550	
(4)ARDN	390	300		400				2,100	
<b>TOTALS</b>				<b>10,222</b>		<b>350</b>		<b>22,050</b>	

**10. SECONDARY TECHNICAL CODES (maximum 6 codes of 3 positions each)**  
 390 520 540 560 590

**11. SECONDARY PURPOSE CODE**  
 500/300

**12. SPECIAL CONCERNS CODES (maximum 7 codes of 4 positions each)**

A. Code	NUTR	TECH	INTR
B. Amount			

**13. PROJECT PURPOSE (maximum 480 characters)**  
 To improve the effectiveness of strategies, programs and projects in the areas of health management, health financing, nutrition, child survival and special concerns in the LAC region by facilitating the exchange and application of technology and information.

**14. SCHEDULED EVALUATIONS**

MM	YY	MM	YY	Final	MM	YY
Interim	10	9	2		09	9

**15. SOURCE ORIGIN OF GOODS AND SERVICES (as permitted under Agency's Buy-America policy)**  
 000  941  Local  Other (specify)

**16. AMENDMENTS/NATURE OF CHANGE PROPOSED (This is page 1 of a \_\_\_ page PP Amendment.)**

This amendment increases the authorized life-of-project by \$350,438 to \$22,050.438. The additional funds will be used for Argentinean Hemorrhagic Fever control activities.

<b>17. APPROVED BY</b>	Signature James Michel <i>for Aaron S. Wilton</i>	<b>18. DATE DOCUMENT RECEIVED IN AID/W. OR FOR AID/W DOCUMENTS. DATE OF DISTRIBUTION</b> MM DD YY 10 19 2005 9 11
	Title AA/LAC	

PROJECT AUTHORIZATION  
(Amendment No. 3)

Name of Country: LAC Regional

Name of Project: Health & Nutrition Technical Services Support

Number of Project: 598-U657

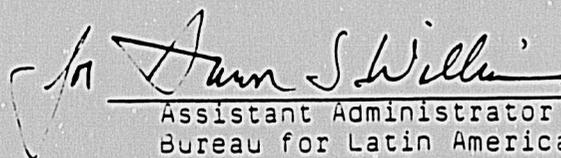
1. Pursuant to Sections 103 and 104 of the Foreign Assistance Act of 1961, as amended, the Health & Nutrition Technical Services Support project was authorized on June 22, 1989 and amended on May 1, 1991 and July 18, 1991. That Authorization is hereby amended as follows:

a. Paragraph 1 is amended to delete the figure "Twenty One Million Seven Hundred Thousand United States Dollars (\$21,700,000)" and to insert in its place the figure "Twenty Two Million Fifty Thousand Four Hundred Thirty-Eight United States Dollars."

b. Paragraph 2 is amended to delete the second sentence and insert in its place the following sentence: "The Project will include the provision of long and short-term advisors, conferences, workshops, intensive studies and analyses and technical assistance and commodity support in response to the cholera and argentinean hemorrhagic fever epidemics in the LAC region."

c. Paragraph 3b is deleted and the following inserted in its place: "Contracts and Cooperative Agreements entered into with LAC Regional funds and Mission buy-in funds to finance activities in furtherance of the project objectives will be limited to a maximum of \$35,350,438 including \$22,050,438 in LAC Regional funds and up to \$13,300,000 in Mission-obligated funds."

2. The Authorization cited above remains in force except as hereby amended.

  
Assistant Administrator  
Bureau for Latin America  
and the Caribbean

9/25/91  
Date

ATTACHMENT 3



PAN AMERICAN HEALTH ORGANIZATION  
*Pan American Sanitary Bureau, Regional Office of the*  
WORLD HEALTH ORGANIZATION

525 TWENTY THIRD STREET, N.W. WASHINGTON, D.C. 20037 U.S.A.

CABLE ADDRESS OFSANPAN

IN REPLY REFER TO HPT/VLR/H6/28/2

TELEPHONE 961-1200

August 30, 1991

Dear Ambassador Michel:

Thank you for your letter of August 20, 1991, informing me that the Agency for International Development (AID) has agreed in principle to provide \$311,200 for the purchase of the vaccine against Argentinean Haemorrhagic Fever. We understand that these funds can be available only in the context of a research project in which the safety, immunogenicity and efficacy of the vaccine will be investigated further.

In response to the three specific points raised in your letter, please note the following:

- a) The Pan American Health Organization (PAHO) is willing to receive a grant from AID to complement the funds provided by the Government of Argentina (GOA) in order to purchase and package the vaccine. Taking into account the figures provided by the Department of Defense (DOD) on the costs of these two items and PAHO's calculations on the cost of transportation of the vaccine, travel of personnel for monitoring the project, and miscellaneous commodities, a total estimate of \$350,483 was determined for the grant (please see attached budget). If DOD absorbs the costs of transportation of the vaccine as it did for its first shipment, then the estimation would be reduced to \$343,691.
- b) PAHO will assist the GOA to develop and review the research protocols and to monitor and evaluate the studies. In addition, PAHO will provide progress reports and a final report to AID.

The Honorable James H. Michel  
Assistant Administrator  
for Latin America and the Caribbean  
Agency for International Development  
Washington D.C. 20523-0092

RECEIVED  
BY LAC/DR/HN

SEP 5 1991

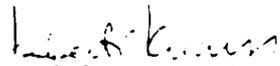
AM PM  
7 8 9 10 11 12 1 2 3 4 5 6

- c) PAHO will waive the overhead charges on this grant and will absorb the cost of salaries of its staff involved in the purchase of the vaccine and in all technical phases related to the research project.

Finally, we are pleased to enclose an outline of the project proposal entitled "Studies on Argentinean Haemorrhagic Fever Vaccine". We trust that the document contains all necessary information required by your Agency for the preparation of the Grant Agreement.

Looking forward to hearing from you, I remain,

Sincerely yours,

  
Carlyle Guerra de Macedo  
Director

Project Title: Studies on Argentine Haemorrhagic Fever Vaccine

Project Location: Argentina (Provinces of Santa Fé, Buenos Aires and Cordoba)

Project Duration: Two years (US Fiscal Years 1992 and 1993).

Implementing Entity: PAHO and the Government of Argentina

Contact Person: Dr. Francisco Pinheiro (202) 861-3271  
Dr. Gabriel Schmunis (202) 861-3272

Date of submission to AID: 30 August 1991

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A. PROJECT PURPOSE AND DESCRIPTION

A.1 Problem Statement

A live attenuated vaccine (Candid-1) has been developed against Argentine Haemorrhagic Fever (AHF). Studies involving some 6,700 human volunteers have shown that Candid-1 is safe, immunogenic and efficacious against AHF. It is essential, however, to confirm such findings in a larger number of Argentine volunteers before implementing a well planned routine vaccination program against AHF. Such program will lead to a drastic reduction in the incidence of this major public health problem in Argentina.

A.2 Project Purpose

The objectives of the project are to validate the immunogenicity and efficacy of Candid-1 and to observe for the occurrence of rare clinical adverse reactions in a large group of volunteers. The main beneficiaries of the study will be the rural population living and/or working in the AHF endemic area.

A.3 General Description of Project and Reason for its Importance

The target population (persons 15 to 65 years old) will be vaccinated and monitored for the occurrence of adverse reactions

following a standard clinical form. The immune response to the vaccine and persistence of immunity will be evaluated in selected subsets of volunteers. Vaccine efficacy will be determined taking into account historical data provided by a Phase III double blind randomized placebo controlled study conducted among Argentine volunteers during 1988-90. The reduction in annual incidence of AHF following widespread vaccination in comparison to incidence over the preceding four years (1988-1991) in a given area to be covered by immunization with Candid-1 will also serve to estimate vaccine protection. Such information will be of great significance since vaccination is the only effective intervention of practical use for the prevention of AHF. The project will be coordinated and managed by the Instituto Nacional de Estudios sobre Virosis Hemorrágicas (INEVH), Pergamino, in close collaboration with health departments of the Argentine provinces where AHF occurs, and under the supervision of the Argentine Ministry of Health.

#### A.4 End of Project Status

The data from this study will provide useful information for planning and implementation of a sustainable wide-scale immunization program against AHF. At the end of the project Argentine investigators will be well informed with respect to the safety and efficacy of the vaccine and will be in a position to make a judgement on the wider routine clinical application of the vaccine in the high risk area.

#### B. PROJECT BACKGROUND

Background: AHF is a severe viral infection that occurs predominantly in the rich farmland of north-central Argentina known as

humid pampa. In most years, 200-400 cases of AHF are seen in this region. However, periodic large epidemics occur involving up to 1,000 individuals. As a consequence, the disease has had a considerable impact on the welfare and economy of Argentina. AHF ranges from a mild flu-like illness to severe disease and death. Typically, fever to 104<sup>o</sup>F or more, headache, loss of appetite, back pain, muscle aches, dizziness, constipation or diarrhea, a skin rash and bleeding gums are seen, and last for 7-10 days. Improvement will begin in most patients during the second week, while those with more severe disease will develop extensive bleeding from the nose, mouth, intestines and/or urinary tract, or a progressive neurological disease with tremors, delirium, ataxia, convulsions and coma. In some patients, a mixture of these severe disease types and shock may occur. The mortality, in untreated cases, is 20-30%. Successful therapy has been developed for AHF through administration of plasma obtained from persons who have had AHF and recovered. Specific antibodies present in the plasma seem to be capable of neutralizing the virus causing AHF. If this immune plasma is administered in therapeutic doses within 8 days after the onset of symptoms, the mortality drops to less than 1%. Unfortunately, this approach is complicated by potential hazards associated with giving blood products, that is, viral hepatitis or other transfusion-borne diseases. Moreover, a curious late neurologic syndrome (generally benign) has been seen 2-6 weeks after plasma administration in 8-10% of patients.

Candid-1 is a live-attenuated vaccine derived from the prototype XJ strain of Junin virus developed at the United States Army Medical Research Institute of Infectious Diseases (U.S.A.M.R.I.I.D.) between

1979 and 1985 under a collaborative project of the Government of Argentina, PAHO and U.N.D.P. The vaccine virus is believed to be attenuated based upon the absence of disease in experimental animals (guinea pigs and Rhesus monkeys), and upon certain laboratory characteristics. A previous AHF vaccine, developed by Argentine scientists in the 1960s, was derived from the same lineage as the present vaccine strain. This earlier vaccine, XJ clone 3, was administered to 636 human volunteers in Argentina nearly 20 years ago but was moderately reactogenic. The current vaccine, Candid-1, has been compared to XJ clone 3 in experimental animal models, and has produced fewer adverse reactions. It is highly immunogenic as very small doses (16 PFU) were required to confer immunity against a lethal virus challenge in Rhesus monkeys.

Studies conducted in more than 6,700 human volunteers between 1985-91 have shown that Candid-1 vaccine is safe and highly immunogenic for humans.

To study the protective efficacy of this vaccine, a total of 6,500 human volunteers from 41 localities of the endemic area of AHF of the Province of Sante Fé were inoculated in a double blind, randomized, prospective trial. Inoculation was conducted over a two-year period.

First cohort:	Inoculation began:	3 October 1988
	Inoculation completed:	14 January 1989
	Total inoculated:	5,927
Second cohort:	Inoculation began:	8 November 1989
	Inoculation completed:	16 December 1989
	Total inoculated:	573
TOTAL INOCULATED:		6,500

These volunteers were followed during two epidemic seasons (1989-1990), and enrollment of cases for purposes of analysis was terminated 31 July 1990. A consensus reached with regard to a case definition of AHF (definite or probable) which included: fever or history of fever coupled with indisputable laboratory evidence of recent Junin virus infection (positive virus isolation and/or unequivocal seroconversion), a total white cell count of less than 2,500 and platelet count of less than 100,000.

On 19 November 1990 a meeting was held at U.S.A.M.R.I.I.D. in order to break the study code. Two primary analyses were conducted to determine vaccine efficacy: one analysis ("A" in the Table below) to determine the efficacy of the vaccine in preventing AHF according to the case definition, and the other ("B" below) in preventing any febrile illness (not necessarily meeting all clinical criteria for AHF) associated with laboratory evidence of recent Junin virus infection.

Results:

Season Inoculated	Inoculated	Total	Cases	
			AHF(A)	Febrile (B)
1988	Vaccine	2968	1	4
	Placebo	2959	20	23
1990	Vaccine	287	0	0
	Placebo	286	2	2
TOTAL	Vaccine	3255	1	4
	Placebo	3245	22	25

p=0.0000028      p=0.000057

VACCINE EFFICACY                      95.5%                      84%

Placebo cases-vaccine cases x 100

Placebo cases

PAHO has been involved in projects related to AHF vaccine since 1979 and has given technical and administrative support to the Argentine Government and to U.S.A.M.R.I.I.D. (the US Department of Defense sponsor for the vaccine).

C. PROJECT ANALYSIS

The present project will expand upon data obtained from previous studies with an investigational vaccine against AHF. Therefore, it will provide necessary information to establish a well oriented immunization program against AHF. In turn, this program should reduce considerably the incidence of the disease, thereby bringing considerable social, health, and economic benefits to Argentina. In addition, experimental studies with non-human primates have shown that Candid-1 vaccine protects against the agent of Bolivian Hemorrhagic Fever (BHF); consequently Candid-1 should be considered for use in Bolivia for the prevention of BHF.

The INEVH has extensive experience in different aspects of AHF including immunization trials. Therefore the INEVH will play a major role in coordinating and conducting the project in conjunction with Argentine Provincial and Federal health agencies.

D. PROJECT DESCRIPTION

D.1 Research

- a) This research will be carried out in Argentina under the exclusive responsibility of Argentinean investigators. It is anticipated that the following staff of the INEVH will play the principal role in the project:

Julio Maiztegui (Director), M.D., M.P.H.  
Delia A. Enria, M.D., M.P.H.  
Ana M. Briggiler, M.D.  
María R. Feuillade, Ph.D.  
Silvana Levis, Ph.D.

- b) The research protocols will be reviewed by an existing PAHO Internal Advisory Committee on Health Research. This committee has long been established by PAHO in order to review investigation protocols to be undertaken in the American Region. In case it is needed, external consultation will be sought in order to review the present project.
- c) Protocols will be submitted for review and approval by the existing PAHO/WHO Ethical Review Committee (PAHOERC). The PAHOERC function is to provide a mechanism for the assessment of ethical implications of research projects involving human subjects. The PAHOERC follows the principles established by the: 1) Helsinki II Declaration of the World Medical Association; 2) the Standards of Conduct for Research carried out by or under the auspices of the World Health Organization;

3) the Council for International Organizations of Medical Sciences (CIOMS) general guidelines and principles, with some exceptions to reflect actual local conditions in the Hemisphere.

The PAHOERC is composed by six PAHO staff members (physicians, lawyer) and one researcher from NIH/Bethesda.

#### D.2 Implementation Plan

At the national level all activities of this project will be implemented by the Government of Argentina. Specifically this includes: a) approval of the protocols by a recognized ethical committee; b) recruitment of volunteers; c) obtaining informed consent from all vaccine recipients; d) administration of the vaccine; e) monitoring of clinical adverse reactions and health care for any volunteer suspected of suffering from a vaccine reaction; f) evaluation of vaccine immunogenicity and protection; g) analysis of data and preparation of reports.

PAHO's role will comprise both technical issues (review of protocols, monitoring and evaluation) and administrative actions (e.g. administration of USAID grant, purchase and shipment of the vaccine). The vaccine will be supplied by the Department of Defense (DOD) on a cost reimbursable basis. Due to the extensive and essential past assistance provided by DOD to the development and testing of the AHF vaccine, it is anticipated that DOD will also provide expertise in several phases of the preparation, implementation and evaluation of the project.

In due time, PAHO will procure the vaccine from DOD and will make the shipments in accordance with its administrative procedures. There will be three shipments of vaccine, each one consisting of 50,400 one milliliter doses of Candid-1 vaccine. In principle the shipments will be made every four months, starting in late November 1991; alternatively the last two 50,400 doses may be combined in a single shipment to be done in July/August 1992.

PAHO's staff will make site visits approximately every six months from the beginning of the project, in order to assess the project's progress.

The following activities will be performed by the GOA.

- a) Preparation of detailed protocols for the study and its approval by a recognized ethical committee.
- b) Implementation of Plan:
  - b.1 Recruitment of volunteers: up to 151,200 men and women, 15 to 65 years of age, residents and/or workers of selected rural localities of the endemic area of AHF of the Province of Buenos Aires, Córdoba and Santa Fé.
  - b.2 Informed consent: Every individual receiving the vaccine will be informed of the objectives of the investigational nature of the project, the objectives of the study, and an informed consent will be signed before the inoculation with Candid-1 vaccine.

b.3 Entry Evaluation and Criteria:

b.3.1 Criteria for inclusion:

- a) Generally healthy men and women, 15 to 65 years of age.
- b) No clinical history of AHF.
- c) No prior history of allergies to the components of Candid-1 vaccine.
- d) Rural residents and/or workers of selected areas.
- e) Sign informed consent.
- f) All women must have a negative serum pregnancy test performed within 48 hours prior to inoculation with Candid-1 vaccine or provide documentation of infertility (e.g. surgical hysterectomy).
- g) No history of chronic diseases.

b.4 Preparation and Administration of Candid-1 Vaccine:

The vials of Candid-1 vaccine will be transported to Argentina on dry ice, and will be stored at  $-40^{\circ}\text{C}$  or below at the INEVH. Once the vaccine has been delivered to the INEVH, that institution will be responsible for insuring its appropriate storage and handling. Then it will be transported to the field inoculation sites on dry ice, and kept at these sites at  $-20^{\circ}\text{C}$  for a period of up to 10 days. At the inoculation sites the lyophilized material will be rehydrated on the day of inoculation and kept at  $+4^{\circ}\text{C}$ . Every participant will be inoculated with a  $10^4$  PFU of Candid-1 virus, by intramuscular injection.

D.3. Monitoring and Evaluation

The following two steps will be essential for the evaluation of infrequent adverse reactions, both of which will be undertaken by the Argentine investigators.

- a) Clinical Evaluation: A passive case detection system will be in place throughout the study period. Any of the participants feeling ill will be requested to go to his local (designated) clinic. Local physicians will have listings of all participants in the study. All participants requiring admission will be sent to the INEVH. All cases with a presumptive diagnosis of AHF will be treated with immune plasma.
  
- b) Laboratory Evaluation: In addition to all routine clinical laboratory examinations, blood samples taken during the acute period from patients admitted at INEVH will be kept at  $-70^{\circ}$  C for viral isolation attempts. Acute and convalescent (30, 60 and 90 days) serum samples will be obtained in all cases, and analysed in ELISA and/or neutralization tests with Junin virus.

The determination of vaccine protection will be done by comparing the annual incidence of AHF in selected areas after the immunization with the incidence in the same areas over the preceding four years (1988-1991).

During PAHO's visits to Argentina at approximately six months intervals, discussions will be held mainly with the staff of INEVH in order to analyze and evaluate the clinical, laboratory and epidemiological information collected by the investigators. Other national health authorities will be also contacted and if necessary interviews will be held with local physicians attending the volunteers.

E. FINANCIAL PLAN AND BUDGET

The following table shows the breakdown of costs by category and by agency)

ESTIMATED COSTS, BY AGENCY

	Source of funds	Total cost (US\$)	USA Fiscal year	
			1992	1993
<b>VACCINE</b>				
a) 151,200 doses (\$2.77/dose)	GOA	108,578	108,578	-
Total cost \$ 418,324	AID	310,246	310,246	-
b) Packing and local transport.	AID	5,400	5,400	-
c) Air freight shipment (Three shipments, Philadelphia/B. Aires)	AID a)	6,792	6,792	-
<b>PERSONNEL</b>				
a) Virologist, 3 1/2 months	PAHO	33,696	16,848	16,848
Secretary, 3 1/2 months	PAHO	11,210	5,605	5,605
Proc. Officer, 1/2 month	PAHO	1,740	1,740	-
b) GOA Personnel	GOA b)	(b)	-	-
<b>TRAVEL</b>				
a) PAHO staff (2 trips/year)				
Air fare (2 round trips/year)	AID	8,000	4,000	4,000
Per diem (15/days/year)	AID	4,000	2,000	2,000
b) STC (2 trips/year)				
Air fare (2 round trips/year)	AID	8,000	4,000	4,000
Per diem (15 days/year)	AID	4,000	2,000	2,000
MISCELLANEOUS (expenditures)	AID	4,000	2,000	2,000
OVERHEAD (waived)	PAHO	45,563	45,563	-
<b>TOTAL</b>				
	GOA b)	108,578	108,578	-
	AID	350,438	336,438	14,000
	PAHO	92,209	69,756	22,453
<b>TOTAL</b>		<b>551,225</b>	<b>514,772</b>	<b>36,453</b>

- a) There is a possibility that vaccine shipment will be made through USA military aircraft, at no charge to the Project.
- b) Other expenses to be incurred by the GOA such as educational campaign, materials (syringes, dry ice) gasoline, etc., are not included in this budget. Also, cost of GOA personnel is not included.

b) Method of Financing and Reporting

Payment under this Grant shall be by means of a Letter of Credit (LOC) in accordance with the terms and conditions of the LOC and any instructions issued by AID's Office of Financial Management. A Financial Status Report will be submitted quarterly no later than 30 days after the end of the period, in an original and two copies to AID and the final report will be submitted within 90 days after the conclusion of the Grant.

F. REPORTING

All reports will be prepared by Argentine investigators, if necessary with the assistance of PAHO staff and PAHO consultants. There will be bi-annual progress reports and a final report which will be submitted by PAHO to USAID.

G. CONDITIONS

The Government of Argentina has already indicated its strong commitment to undertake an immunization program with Candid-1 vaccine (see enclosure). If required by USAID a formal and specific approval from the Government of Argentina will be sought by PAHO.

PAHO will be committed to provide technical, administrative and financial resources (salary of staff, waiver of overhead costs, etc.). Similarly, the Government of Argentina will commit personnel (investigators, health workers, administrators) and funding (sharing of vaccine purchase, local costs).