Establishing hepatitis C patients' surveillance system in the Republic of Armenia

Master of Public Health Integrating Experience Project

Community Service Grant Proposal Framework

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List of Acronyms

HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
AIDS	Acquired Immune Deficiency Syndrome
WHO	World Health Organization
NCDC	National Center for Disease Control
RA	Republic of Armenia
MOH	Ministry of Health
USA	United States of America
CDC	Center for Disease Control
HBsAg	Hepatitis B surface antigen
EU	Europian Union
EC	Europian Commission
NGO	Non-Governmental Organizations
RNA	Ribonucleic Acid
PCR	Polymerase Chain Reaction
IU	International Unit
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
HCV RIBA	Hepatitis C Virus Recombinant Immunoblot Assay
NAT	Nucleic Acid Test
IgM	Immunoglobulin M
IgG	Immunoglobulin G
Anti-HBc	Hepatitis V core antigen
EIA	Enzyme immunoassays
SGPT	Serum glutamic pyruvic transaminase
DAA	Direct antiviral agents

PEG-IFN	Pegylated interferon
RBV	Ribavirin
NS	Nonstructural protein
CPP	Cost per patient
CPSVR	Cost per sustained virologic response
SVR	Sustained virological response
HTML	HyperText Markup Language
ID	Identity
CJSC	Closed Joint State Company
PPV	Positive predictive Value
DALY	Disability Adjusted Life Years
YLL	Years of Life Lost
YLD	Years of Lost due to Disability
ICER	Incremental Cost-Effectiveness Ratio
IRB	Institutional Review Board/Committee on Human Research

Executive Summary:

Objectives: The aim of the study is to propose establishing a surveillance system for hepatitis C infection in Armenia. This will rationalize collection and analysis of data, estimate the burden of the disease, and contribute to developing and conducting effective public health policy and intervention for prevention and timely treatment of hepatitis C infection.

Introduction: In 2015, more than 185 million people around the world were infected with hepatitis C virus (HCV), of whom 350 000 die each year. In 2015, viral hepatitis was the 7th leading cause of mortality in the world. During the last decades, HCV infection demonstrates an increasing trend in Armenia. In 2013, the prevalence of HCV among general population was 3-5%. The treatment of chronic HCV infection is focused on preventing further damage to liver to avoid life-threatening complications. There are two strategies for HCV treatment: using a combination of interferon and ribavirin or direct antiviral agents (DAA). Armenia uses the first one, and no DAA medication is registered in the country. The state does not pay for the therapy of HCV while the cost of treatment in the local market is up to 16,000 US$ per person.

Methodology: The proposal suggests to establish surveillance system of HCV infection in Armenia consisting of six components: 1) case definition (clinical (EU 2008/426/EC standard) and laboratory standardization), 2) case reporting (demographic characteristics, clinical data, date, laboratory markers, potential source of inflammation and risk factors), 3) routine case detection and data collection (via electronic software), 4) analysis (epidemiological (incidence and prevalence) and specific (treatment costs, co-morbidities, etc.) reports) 5) dissemination of results among key policy and decision makers and 6) recommendations for further actions (treatment, development of national guideline, educational programs). The evaluation of the project is focused on the quality of the surveillance system (completeness and validity).

Budget: The budget for the first year is estimated as 592,132,310 US$, and the annual budget for the second and following years is expected to be at least 11,363,090 US$.

1. Objectives

The aim of the study is to propose establishing a surveillance system for hepatitis C infection in Armenia. Developing a national surveillance system for hepatitis C virus infection could provide a useful tool for estimating the burden of the disease and following the trend of the disease in the Republic of Armenia. The surveillance system will rationalize collection and analysis of data on the incidence of hepatitis C infection. Information gained from the system can be used to:

- Detect high-risk population groups

- Identify clusters or outbreaks of hepatitis C

- Identify sources of exposure to prevent further transmission

- Identify geographic areas where public health intervention should be conducted

- Develop and conduct effective public health policy and intervention.[1]

2. Introduction

2.1 Prevalence and incidence in the world

Hepatitis C is an infectious disease caused by the hepatitis C virus (HCV).[2] According to recent estimates, in 2015, more than 185 million people around the world were infected with HCV, of whom 350 000 die each year.[2–4] In September 2015, the World Health Organization (WHO), World Hepatitis Alliance and the Scottish Government organized the First World Hepatitis Summit. They issued the Glasgow Declaration on hepatitis which states that there are 400 million people in the world living with hepatitis C and B infections, and 1.4 million people die every year from complications of viral hepatitis in the world.[5,6] In 2015, viral hepatitis was the 7th leading cause of mortality in the world.[6]

There is a geographical difference in the patterns of Hepatitis C infection.[3,7] The prevalence of HCV is low in high-income countries (North America, Western Europe, and Australia). The highest incidence rates of HCV are estimated in middle- and low-income countries in Africa and Central and East Asia.[3,7]

2.2 Situation in Armenia

2.2.1 Prevalence

Armenia, a lower-middle income country, had a 3-5% prevalence of HCV among the general population in 2013.[8–11] It is the third highest rate among post-Soviet countries (Georgia 6.7% and Uzbekistan 6.5%).[11] Of the patients infected with hepatitis C in Armenia, 44% have HCV genotype 1, 37% have genotype 3 and 19% have genotype 2.[8,9,12] The prevalence of HCVamong different groups is:

−   injecting drug users 64.0%

−   imprisoned persons 36.3%

−   patients getting hemodialysis 29.4%

−   commercial sex workers 10.2%

−   patients with tuberculosis 9.0%

−   healthcare workers 6.8%

−   oncological patients 3.1%

−   healthy population 3.6%.[8,9]

2.2.2 Management of hepatitis B, C

In 2015, the Minister of Health of the Republic of Armenia approved the order N3691-A "Methodological guideline for epidemiological management of viral hepatitis B, C".[10] The methodological guideline is for:

- All the medical institutions that provide medical care and services for detection and further management of viral hepatitis C, B cases in the whole territory of the Republic of Armenia

- Professionals of the National Center for Disease Control of the Republic of Armenia, who are included in epidemiological control of hepatitis C, B.

The epidemiological control of viral hepatitis C and B is done by the National Center for Disease Control of the Republic of Armenia (NCDC), which provides methodological management of prevention and regular control activities of HCV and HBV infections in each geographical area including registration and reporting of acute, first time accrued chronic viral HCV infection, HBV cases, and Anti-HCV positive blood persons. The registration form ("Registration form of infectious and parasitic diseases") is approved by N21-n order of the Minister of Health of RA issued on 20.10.2008.[33]

2.2.2.1 Case detection and data collection

According to the methodological guideline, detection of Hepatitis C, B is done by health care workers (not specific infectious disease specialists or hepatologists) in the medical institutions.

The detection criteria are:

- Clinical – anti-HCV positive[13]

- Epidemiological - anamnesis, contact with hepatitis C, B patient, blood transfusion, invasive interventions.

- Laboratory - quick test (presence of HCV antibodies in the blood) and nucleic acid test for HCV RNA.

Patietnts with antibodies of HCV in the blood need to undergo laboratory tests to detect peresence of HCV RNA in the blood. Patinents with possitive answer are determined as patients with chronic hepatitis C infection. Patients with negative answer are determined as patients with acute hepatitis C infection. These patients with acute hepatitis C need to do HCV RNA test at least during two years, every six months.[10]

According to the guideline, the diagnosis should be set within 14 days for organizing and implementing successful treatment, epidemiological and preventative events on time. Anti-HCV positive persons, who are HCV-RNA negative should regularly test for two years but not less than once in six months. The guideline states that there are groups (Appendix 1) of people from three spheres who should do mandatory Anti-HCV test to find the antibodies in the organism and there are some groups who should do mandatory Anti-HCV and HCV RNA tests:

- Transplantation (before taking donor substance)

- Donor service (testing blood for urgent blood transfusion when there is no information about anti-HCV and Hepatitis B surface antigen (HBsAg) screened donor blood)

- Hospital admission departments (for emergency medical intervention).[10]

2.2.2.2 Case registration and case reporting

After detecting cases with hepatitis C infection, the health care worker registers the epidemiological indicators (information about epidemiological anamnesis, contact with a person

infected with HCV, hemodialysis, and information about invasive procedures) in the medical card of the patient.[14] Case registration and reporting of hepatitis B and C is approved by the order of Ministry of Health N 35-N issued on 17.12.2010.[15] The chief of the medical institution is responsible for case reporting.

2.2.3 Future actions

HCV professionals from MOH now work on the project "The National strategy and list of events for fighting against viral hepatitis C in Armenia 2016-2020" which consists of nine strategies:

1. Development of national strategy and support to fighting against HCV at the governmental level. The objective of the strategy is to strengthen the integrated system of anti-HCV actions, planning coordination, management, financing and monitoring at national and local levels.

2. Development and implementation of treatment strategy corresponding to the international approaches at all levels.

3. Development and implementation of a system for HCV treatment medications use corresponding to the international methodology.

4. Ensuring the occupational safety among healthcare workers in terms of being protected from getting HCV. The objective of the strategy is the reduction of cases of nosocomial infection among healthcare workers.

5. Development of laboratory control system of viral HCV. The aim of the strategy is to ensure the continuous process of diagnosing and early detection of HCV.

6. Improvement of epidemiological control of HCV.

7. Strengthening cooperation with the HIV / AIDS national program to fight against Hepatitis

C / HIV combined infection. The objective of the strategy is to prevent transmission of HCV

among HIV / AIDS patients.

8. Development of HCV campaign on health education and healthy lifestyle in the population.

9. Monitoring and evaluation of program implementation (Melik-Andreasyan G., MD, Ph.D.,

ScD, Professor, Director of The Research Institute of Epidemiology, Virology and Medical

Parasitology after A.B. Alexanian, oral communication, 30 March 2016).

2.3 Natural history of HCV infection

Hepatitis is a term that is used to describe inflammation of the liver which can be caused

by hepatitis viruses (the main cause of hepatitis), other toxic substances (e.g. alcohol or some

drugs) and some autoimmune diseases.[2,16] The HCV is a RNA (ribonucleic acid) virus which is

highly mutable.[17] The genome analysis of the virus has identified at least six genotypes (1, 2, 3,

4, 5, 6) but only four of them (1, 2, 3, 4) are common.[17] The genotype is particularly important

as it determines the duration of the treatment and the medications for the therapy.[4,17,18] The

distribution of genotypes is different in various countries. In the United States, 70% of the

disease is caused by genotype 1, meanwhile, in the Middle East 91% of the patients are infected

with the virus of the genotype 4.[3] Having multiple genotypes makes the development of a

vaccine very challenging,[17] and there is no hepatitis C vaccine nowadays.[19] A person can be

infected with multiple genotypes simultaneously.

Hepatitis C causes acute (symptoms of HCV infection appear within six months of

acquiring infection) and chronic (symptoms of HCV infection appear six months or later after

acquiring infection) infection.[4] Approximately 20% −30% of infected persons develop

symptoms of acute illness such as fatigue, abdominal pain, poor appetite, or jaundice (yellowing

of skin and the whites of the eyes).[20] According to the Center for Disease Control (CDC) and

Prevention of the United States of America (USA), of those infected with HCV:

- 75–85% develop chronic infection

- 60–70% develop chronic liver disease

- 5–20% develop cirrhosis over a period of 20–30 years

- 1–5% die from the consequences of chronic infection (liver cancer or cirrhosis).[20]

About 15% of people who have been infected and have strong immune system can

spontaneously eliminate the infection without treatment, and anti-HCV antibodies will stay in

their organism during their whole life.[18,19] The others with weaker immune system will remain

infected, and the virus will continue living in the cells of the human body.[17]

Being infected is initially asymptomatic until liver failure becomes clinically expressed

and available assays do not distinguish acute from chronic infection.[18] About 60-80% of patients

infected with acute HCV do not feel any symptoms.[18,19] Only some patients with acute infection

may exhibit fever, fatigue, decreased appetite, nausea, vomiting, abdominal pain, dark urine,

grey-colored faces, joint pain and jaundice.[19] Chronic HCV infection can cause liver failure,

liver cirrhosis, and hepatocellular carcinoma.[21] The natural progression of hepatitis C infection

is described in Appendix 2.[22]

2.4 Transmission of HCV

The most expedient way of virus transmission is blood (e.g. renal dialysis and unscreened

blood transfusions, use of unsterile needles and contaminated drug solutions, cosmetic

procedures (such as tattooing and body piercing)). People can also be infected by mucosal

exposures to blood or serum-derived fluids (e.g., birth to an infected mother, unprotected sexual

relations with infected partner).[4,7,19] Hepatitis C is not transmitted via breast milk, food, water and/or by casual contact, such as hugging, sharing food or drinks with an infected person.[18]

2.5 Vulnerable groups

According to the WHO, there are groups of people who are vulnerable to being infected with HCV:

- Individuals who received blood transfusions without HCV blood screening

- Intravenous drug users

- Patients on dialysis

- Health care workers (where there is a risk of HCV transmission)

- Babies born to mothers known to be infected with HCV

- Regular sexual partners of patients infected with HCV

- Persons with Human Immunodeficiency virus (HIV) infection

- Prisoners and previously incarcerated persons

- Individuals who received medical or dental treatment where infection control may be poor

- People who have tattoos, body piercing, and other procedures dealing with blood of different clients (such as manicure or pedicure).[2,4,7,16,18,19,23]

2.6 Screening/Diagnosis

Since in the majority of cases the infection has no symptoms, usually people get tested when they already have the chronic HCV infection. The process of liver cell damage may continue long years after initial infection.[24]

The screening process consists of two steps: 1) to identify the presence of anti-HCV antibodies in order to detect if the person has ever been infected with the virus or not; 2) to conduct a Polymerase chain reaction (PCR) test - a nucleic acid test for HCV RNA to establish whether the individual has chronic HCV infection or not, and if the infection is present the genotype of the infection.[18] Prices of the tests available in Armenia are presented in Appendix 3.

2.6.1 Clinical definition - EU 2008/426/EC standard

Acute HCV infection: either a documented negative HCV antibody laboratory test result followed within 6 months by a positive test (as described in the laboratory criteria for diagnosis) or an acute illness with a discrete onset of any sign or symptom consistent with acute viral hepatitis (e.g., anorexia, abdominal discomfort, nausea, vomiting), and either a) jaundice, or b) serum alanine aminotransferase (ALT) levels >400 IU/L.[1,25–28]

Chronic HCV infection: most HCV-infected persons are asymptomatic; however, many have chronic liver failure, which can range from mild to severe.[1,25–28] Hence, there are no clinical diagnostic criteria for chronic HCV infection.

2.6.2 Laboratory diagnostic criteria for HCV infection

The laboratory diagnostic criteria for acute HCV include one or more of the following:

1.   Anti-HCV screening test (identifying antibodies to hepatitis C virus) positive with a signal to cut-off ratio predictive of a true positive as determined for the particular assay as defined by the Center for Disease Control and Prevention of the United States of America, or

2.   Hepatitis C Virus Recombinant Immunoblot Assay (HCV RIBA) positive, or

3.   Nucleic Acid Test (NAT) for HCV RNA positive and, meets the following two criteria:

    A. IgM (Immunoglobulin M) antibody to hepatitis A virus (IgM anti-HAV) negative

B.   IgM antibody to hepatitis B core antigen (IgM anti-HBc) negative.[1, 14, 19, 20]

The laboratory criteria for chronic HCV include one or more of the following:

- Anti-HCV positive (repeat reactive) by EIA (enzyme immunoassays), verified by an additional more specific assay (e.g., RIBA for anti-HCV or nucleic acid testing for HCV RNA),

- HCV RIBA positive,

- Nucleic acid test for HCV RNA positive,

- Report of HCV genotype,

- Anti-HCV IgM

- Anti-HCV IgG (Immunoglobulin G) avidity index

- Observation of serial changes in viral load (viral load fluctuations >1 log and HCV RNA levels <100,000 IU/mL)

- Anti-HCV positive with a signal to cut-off ratio predictive of a true positive as determined for the particular test as determined and posted by CDC.[1,25–32]

According to these criteria, CDC classifies cases into two groups: confirmed and probable. Confirmed acute HCV is the case that meets the clinical case definition and is laboratory confirmed, and is not known to have chronic hepatitis C.[1,25–28] Confirmed chronic HCV is the case that is laboratory confirmed and that does not meet the case definition for acute hepatitis C.[1,25–28] Probable is the case that is anti-HCV positive by EIA and has alanine aminotransferase (ALT or SGPT(Serum glutamic pyruvic transaminase)) values above the upper limit of normal, but the anti-HCV EIA result has not been verified by an additional more specific assay or the signal to cut-off ratio is unknown.[1,25–28]

2.6.3 Follow-up screenings

After being diagnosed with HCV, patients need to take routine test to monitor the effects of the treatment. Each 6 weeks patients need to check ALT and AST levels and do HCV RNA test. After successfully finishing the treatment patients need to do HCV RNA test twice; 6 months and 2 years after the treatment is over.[33]

2.7 Treatment

The treatment of chronic HCV infection is focused on preventing further damage to liver in an effort to avoid life-threatening complications, including liver cirrhosis, liver failure, and premature death.[34] After the treatment, the damaged cells do not come back to their previous condition.[22] The treatment is more effective in the period of acute infection, so the sooner the patients get tested, the cheaper and more effective the treatment can be.[4,35]

The treatment of Hepatitis C virus infection and medication for this are changing rapidly. Before the investigation of the first representatives of direct antiviral agents (DAA),[36] the treatment was based on the therapy with interferon and ribavirin for 24-48 weeks (depending on the genotype of the infection).[35,37] Pegylated interferon (PEG-IFN) and Ribavirin (RBV) are recommended for 48 weeks in those with genotype 1 and 4 HCV infection (patients with or without liver cirrhosis).[2,4,38] PEG-IFN and RBV are recommended for 24 weeks in those with genotype 2 or 3 HCV infection (patients with or without liver cirrhosis).[38]

Currently, treatment therapies are based on the interferon-free model.[35,37,38] As of October 2015, there are 4 classes of DAAs licensed for treatment of HCV:

- Protease (nonstructural protein 3/4A (NS3/4A)) inhibitors (Asunapevir, Paritavepir, Simeprevir)

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- Nonstructural protein 5A (NS5A) inhibitors (Daclatasvir, Ledipasvir, Ombitasvir)

- Polymerase (nonstructural protein 5B (NS5B)) inhibitor nucleoside analog (Sofosbuvir)

- Polymerase (nonstructural protein 5B (NS5B)) inhibitor, non-nucleoside analogue (Dasabuvir).[38]

In persons with HCV infection and without cirrhosis DAA are recommended for 12 weeks in those with genotype 1, 2, 3, 4 infection.[38] In persons with HCV infection and with cirrhosis DAA are recommended for 24 weeks in those with genotype 1, 2, 3, and 4 infection.[38]

In 2013, when DAA therapy was introduced in the USA, the wholesale acquisition drug price to treat one person was 84 000 US$.[38] Prices in the United States have since come down up to 50 000 US$ as a result of negotiated discounts.[38] A number of countries (e.g. India, Bangladesh) have obtained access to DAA therapy at much lower prices due to direct negotiations with the manufacturers and by the introduction of generic medicines.[39] Generic formulations of Sofosbuvir are coming to the market at a price below 900 US$/patient for 12 weeks of treatment, with anecdotal reports of even lower prices (e.g. 500 US$ /patient for 12 weeks) in India.[39]

WHO's latest guideline for the screening, care and treatment of persons with HCV infection presents the estimated cost per patient (CPP) and cost per sustained virologic response (CPSVR) for PEGylated interferon/ribavirin and DAA in three countries (Brazil, Mongolia, Ukraine) (Appendix 4).[38] Sustained virologic response (SVR) is defined as a viremia 24 weeks after completion of antiviral therapy for chronic HCV infection.[39] Appendix 5 presents estimated total cost of treating all persons diagnosed with chronic HCV infection in Brazil, Mongolia, and Ukraine (2015 US$) with DAA regimens.[38]

2.7.1 Treatment in Armenia

Currently, Armenia uses the model of combination of interferon and ribavirin. No DAA medication is registered in the Republic of Armenia.[40] The registered medications for HCV treatment have generic name "ribavirin", "peginterferon alfa-2b" and "peginterferon alfa-2a".[40] Appendix 6 presents prices of all HCV treatment medications available in Armenia.

Generally, the Republic of Armenia covers expenses of some medications registered in Armenia. These medications are from two lists: "The list of basic medications for the Republic of Armenia"[41] and "The list of life needed low-demand medications ".[42] Medications not included in the list are not paid by the government.

HCV treatment medications are not included in "The list of basic medications for Republic of Armenia"[41] or "The list of life-needed low-demand medications".[42] These facts show that the government does not pay for the treatment of HCV infection and patients should pay for their treatment. In the local market, the treatment can cost up to 16 000 US$ per 48 weeks.[11]

2.8 Surveillance systems

"Public health surveillance is the ongoing, systematic collection, analysis, interpretation, and dissemination of data about a health-related event for use in public health action to reduce morbidity and mortality and to improve health."[43] Data disseminated by the public health surveillance system can be used for immediate public health action, program planning, evaluation, and formulating research hypotheses.[26] Data from a public health surveillance system can be used to:

- guide immediate actions for cases of public health importance;

- measure the burden of a disease (or other health-related events), including changes in related factors, the identification of populations at high risk, and the identification of new or emerging health concerns;

- monitor trends in the burden of a disease (or other health-related events), including the detection of epidemics (outbreaks) and pandemics;

- guide the planning, implementation, and evaluation of programs to prevent and control disease, injury, or adverse exposure;

- evaluate public policy;

- identify modifications in health practices and the effects of these changes;

- prioritize the allocation of health resources;

- describe the clinical course of disease; and

- provide a basis for epidemiologic research.[26]

According to World Health Organization (WHO) standards, all the surveillance systems should consist of six main components:

- detection of health event

- investigation and confirmation (epidemiological, clinical, laboratory)

- collection of data

- analysis and interpretation of data

- feedback and dissemination of results

- specific actions for prevention and control.[44]

An effective system of public health surveillance must be simple, acceptable, sensitive, timely, flexible and also representative to be effective in public health actions.[45] Furthermore, it

is highly recommended that establishing a surveillance system in developing countries such as Armenia should be less complicated, more straightforward to establish to make it sustainable.[46]

The surveillance system has three objectives:

1. to measure and detect disease burden

2. to detect outbreaks

3. to simulate research projects.

3.Methodology

3.1 Conceptual framework

Establishing hepatitis C patients' surveillance system is a long-term intervention, which requires collaboration between different types of institutions inside the country (internal), as well as outside the country (external). The project involves all the stakeholders such as Ministry of Health, National Center for Disease Control and Prevention, medical institutions (public and private laboratories and clinics), NGOs, research institutions, tattoo/piercing and beauty salons, HCV patients, and other stakeholders. The conceptual framework of hepatitis C patients' surveillance system demonstrates that the project implementation should pay attention to case detection, registration, reporting, confirmation, analysis and feedback (see Appendix 7).[47]

3.2 Implementation plan synopsis

3.2.1 Public Health Surveillance

We propose to establish a surveillance system for hepatitis C infection in Armenia to provide a useful tool for estimating the burden of the disease and following the trend of the disease in the Republic of Armenia. For that, the following activities are proposed to implement in Armenia.

3.2.1.1 Case definition

This proposal suggests using a standardized case definition for HCV infection in Armenia in accordance with the international standards for Clinical definition (EU 2008/426/EC standard) and Laboratory criteria of HCV infection.[1,17,23,25,27,28,33,48]

3.2.1.2 Case registration

This proposal suggests using a standardized case-reporting form. The information included in the form should be available from patient's medical records. The standardized form should contain information that belongs to six main domains:

- Demographic (name, address, phone number, date of birth, sex, occupation, ethnic group, pregnancy status of women)

- Clinical data (abnormal liver function tests, jaundice, asymptomatic)

- Dates (onset of HCV, diagnosis, reporting/notifying)

- Laboratory markers (Hepatitis C RNA, anti-HCV and confirmation that the case is considered acute (i.e. meets case definition) or chronic, genotype of chronic HCV)

- Exposure - questions to find out where the patient could acquire the infection

- Risk factors (injecting drug use, sexual contact (homosexual/heterosexual), receipt of blood transfusion/blood product, acupuncture/tattooing/body piercing, dialysis, surgical or dental procedure, hemodialysis, hospitalization).[27,46,48–50]

3.2.3 Case Reporting/Data Collection/Data Source

The proposal suggests having standardized protocol for case-reporting and data collection. The first step of data collection will start from the primary health care sector:

polyclinics. In a case of suspecting the presence of hepatitis C infection (based on the clinical indicators), physicians refer these individuals to the laboratory for testing. After defining the presence of HCV doctors will refer these patients to the hospitals for further treatment, follow-up tests, and care. The case registration and reporting will be done only by the physicians of hospitals after being admitted. The doctors will mandatory register these patients in the database and give ID to each patient. The doctors will report to the NCDC about HCV cases. The format of reporting should be electronic. The proposed process of case-reporting is described in Appendix 8.

3.2.4 Analysis and Dissemination of results

Before the surveillance data can be interpreted, it must be organized and analyzed. The analyzing staff should use the software for compiling and analyzing the information.

3.2.4.1 The analyzing staff

The highest level analysis of the data collected in the software should be done mainly by monitoring and evaluation specialists of the National Center of Disease Control and reported to the MOH. The information should be reported as general epidemiological information including:

- prevalence
- incidence and specific reports including:
    - demographic characteristics of patients with HCV
    - co-infections or co-morbidities
    - source of infection (probable or established)
    - adverse effects of HCV treatment medications

- treatment outcomes

- treatment cost

- treatment coverage

3.2.4.2 Frequency of reports

The indicators on the incidence and prevalence of HCV should be prepared by NCDC of Armenia and reported to the MOH (Demartment of Public Health) monthly. NCDC of Armenia should prepare summaries on demographic characteristics of patients with HCV, co-infections or co-morbidities, probable or established source of infection, adverse effects of HCV treatment medications, treatment outcomes and treatment cost and report to the MOH (Demartment of Public Health) quarterly. To have overall description of the situation, the NCDC of Armenia should present annual report on HCV situation in Armenia, which includes all the reports presented during the year. The annual report should be publicly available on the web-site of the NCDC.

3.2.5 Electronic managing of the surveillance system: HCV-Manager

The processes of case registration, case reporting and analysis should be electronic. In order to arrange electronic processing, we propose to develop new software to make the process less complicated, fast and more reliable.

3.2.5.1 Description of the software

The software called HCV- Manager should be a web-based tool for managing all the information needed for HCV control programs. It should integrate data across all aspects of HCV control including information on suspects, patients, medicines, laboratory testing, diagnosis, treatment, and outcome. One of the advantages of the tool will be the integration of

all kinds of information necessary for HCV management from patient to the country level. The

system will allow recording of clinical and laboratory results and provide data for treatment

adherence. The tool will provide an opportunity for monitoring medicine safety and

effectiveness at the patient level by tracking side effects of HCV treatment medicines. The tool

will provide easy methods for analyzing collected data and exporting data to other statistical

programs. Reports which can be produced from the storage database can have an impact on

future policy, strategies and decisions. Through the tool, specialists can measure HCV burden in

Armenia. The newly developed software will allow calculating the overall cost of the treatment

for each patient.

3.2.5.2 *Software requirements*

To use the application, the users (personnel of the health facilities authorized to enter,

register, edit, monitor, and validate data) must have their unique login and password and be

equipped with:

- A computer with Internet connection

- A network connection to the system (Internet access is required only if the system is
based on an Internet server)

- An HTML (HyperText Markup Language) browser (e.g., Google Chrome, Internet
Explorer, or Mozilla Firefox)

- Enabled JavaScript in browser

3.2.5.3 *Users who should have access to the software*:

- HCV physicians

- Laboratory personnel

- MOH staff

- The National Center for Disease Control and Prevention staff

- The staff of the Research Institute of Epidemiology, Virology and Medical Parasitology named after A.B. Alexanian

Every user in the proposed system should be assigned to a profile. The profile is a set of permissions that indicates what the user can or cannot do in the system. Each user of the software has to have different responsibilities (Appendix 9) and different level of access to the information provided by the HCV-Manager.

- **HCV physicians** will have full access to the management of their cases in the proposed system. They will have an opportunity to register new HCV cases in the system (name, address, phone number, date of birth, sex, occupation, social security number, ethnic group, pregnancy status of women, onset of HCV, diagnosis, reporting/notifying , information about the probable/established source of inflammation, risk factors (injecting drug use, sexual contact (homosexual/heterosexual) with HCV patients, receipt of blood transfusion/blood product, acupuncture/tattooing/body piercing, dialysis, surgical or dental procedure, hospitalization), medicines used, doses, frequency and duration of treatment, side effects of the medicines, outcome of the treatment). The physicians will have access to modify the treatment scheme of cases (i.e., medicines or doses substitution). Physicians will give an account and an ID (identity) number for each registered patient in the proposed system. After filling all the required information for registering a new case, the database will compare the new registered case's characteristics with already registered ones. After comparing the cases, the software will give

information about with the same name and birth date. The software will ask the permission of the physician to register the new case. This will allow to avoid double registration of the same case.

- **Laboratories** in Armenia that conduct HCV tests will have an account in the proposed software. They should use the software to add laboratory test results only for those cases already registered by the hospitals (they will not be allowed to register new cases to avoid duplicate registrations). The laboratory should fill the information about laboratory markers (Hepatitis C RNA, quantity of HCV-antibodies in blood, genotype of chronic HCV, PCR, HCV RIBA, ALT, and AST) according to the ID number of the patient. However, to avoid technical mistakes with ID numbers and to be able to contact a patient when needed, the laboratories should have access to some socio-demographic characteristics of the patients (name, phone number, age, sex) as well.

- **The Ministry of Health Department of Public Health** will have access to the whole data. The department cannot modify the information registered in the database.

- **The National Center for Disease Control and Prevention** will have access to the whole information of the country but should not have access to add/remove/modify any information. The proposed tool will give them opportunity to make reports, monitor and analyze the situation in the country.

- **The Research Institute of Epidemiology, Virology and Medical Parasitology named after A.B. Alexanian** will have limited access to the software. Persons who work specifically in the analysis of HCV data should use data with patients ID. The users should not see the name,

address or phone number of patients, add/remove/modify any kind of information. The tool will give them opportunity to make reports and use them in their further research.

All other institutions or researchers should have access (making reports only) to the database only with the permission of the MOH with temporary accounts that will be deactivated after the end of the research/program. These temporary users should not have access to the names, adresses or phone numbers of patients. The system should show only ID numbers of patients.

3.2.5.4 *Structure of the software*

In order to use the software, users should log in every time. After the user completes the login page, the system should welcome and redirect the user to the homepage. On the home page, users should find the system's main menu. It should contain the six main functionalities of the system:

- *Cases* – This should allow the user to search, notify, follow-up medical information on cases. The function should be available for physicians, laboratories (partially), patients, hospitals, MOH, National Center for Disease Control and Prevention , Research Institute of Epidemiology, Virology and Medical Parasitology named after A.B. Alexanian (not the whole) and other research institutuions/researchers with limited temporary access.

- *Medicines* – This should allow the user to record, search information about the medicines. This function should be available for physicians, patients, hospitals, MOH, National Center for Disease Control and Prevention, Research Institute of Epidemiology, Virology and Medical Parasitology named after A.B. Alexanian and other research institutions/researchers with limited temporary access.

- *Management* – This should allow the user to generate, search, and print reports, indicators. This function should be available for physicians, hospitals, MOH, National center for disease control and prevention, Research Institute of Epidemiology, Virology and Medical Parasitology named after A.B. Alexanian and other research institutions/researchers with limited temporary access.

- *Administration* – This should allow the system administrator to manage the system to include, remove, and change users, health system structure, medicines, treatment regimens, and other elements. This function should be available for physicians, hospitals, MOH.

- *Settings*-The section should allow to modify the password of the user and language (Armenian, Russian, and English). This function should be available for all the users.

- *Search*-The section should give opportunity to search information by keywords. This should be available for all the users.

The software should be available in three languages most frequently used in Armenia (Armenian, English, and Russian). In order to make the reports more comfortable and available in three languages, during the filling of the information users should choose answers for questions from the list that will suggest software and only for some questions the system should allow to type the answer if the physician has additional point (probable source of inflammation, side effects of medicine). In this case, the physician should fill the information in three languages.

3.2.5.5 Training of software users

The users of the software (infectious disease specialists, hepatologists, chief physicians of laboratories, monitoring and evaluation professionals of the National Center of Disease Control,

the staff of the Research Institute of Epidemiology, Virology and Medical Parasitology named after A.B. Alexanian) dealing with HCV will be trained by the software trainer. The company which develops the software will provide qualified trainer for the trainings. The proposed trainings will be organized in big cities of the country, one city from each marz (marz centers). One-day (5 hours) training sessions will be conducted in each of these cities besides Yerevan, where these trainings will take place four times to cover all the personnel who need the training.

Training Description: This training will prepare infectious disease specialists, hepatologists, chief physicians of laboratories, monitoring and evaluation professionals of the National Center of Disease Control, and the staff of the Research Institute of Epidemiology, Virology and Medical Parasitology named after A.B. Alexanian) dealing with HCV to effectively use current software (HCV-manager). It will provide skills to manage medical history of patients with HCV, develop effective reports and monitor overall situation in Armenia. Trainings will be organized in the institutions with computers having access to the internet.

Training Objectives

- By the end of the training the physicians (infectious disease specialists, hepatologists) will be able to use the main functions of HCV-manager by registering, modifying, and managing information necessary for HCV patients' treatment and management.

- By the end of the training chief physicians of laboratories will be familiar with all the functions of the HCV-manager and use the software according to their needs and responsibilities (registering the laboratory analyses results).

- By the end of the training monitoring and evaluation professionals of the National Center for Disease Control will be familiar with all the functions of the HCV-manager, make their reports on HCV using the software and monitor the situation in Armenia.

- By the end of the training staff of the Research Institute of Epidemiology, Virology and Medical Parasitology named after A.B. Alexanian) dealing with HCV will be familiar with all the functions of HCV-manager and use the reports from the software for their further research and needs.

Training Schedule: The schedule of trainings is presented in Appendix 10. The total duration of the trainings is 300 minutes. Trainigs will take place from 11:00 am to 16:30 pm with a 30 minute break.

*Training Outcomes***:** By the end of this course, the participants will be able to:

1. Register a patient online

2. Enter the demographic characteristics of a patient

3. Enter the medical history of a patient

4. Enter the results of laboratory analyses of a patient

5. Enter the strategies of treatment

6. Enter the list of treatment medications

7. Enter the side effects

8. Monitor the dynamics of the treatment

9. Monitor the treatment outcomes of patients

10. Analyze the information recorded in the software

11.   Develop standard reports for each medical institution, for each city, for each marz and the whole country, on:

- incidence of HCV infection

- prevalence of HCV infection

- demographic characteristics of the cases

- rates of co-infections or co-morbidities

- contamination origins (probable or established)

- rate of adverse effects

- rate of treatment outcomes

- treatment history

- case management (dates of analysis)

12.   Monitor the HCV- treatment strategies in different areas of Armenia and the whole republic

13.   Search for information in the software.

3.2.2 Public Health action

Primary prevention of the infection with vaccination is currently unavailable.[19] The WHO suggests actions for HCV infection prevention for two specific spheres such as health care settings and sexual transmission. The suggested measures in health care settings include:

- Hand hygiene: including surgical hand preparation, hand-washing and use of gloves

- Safe handling and disposal of sharps and waste

- Safe cleaning of equipment

- Testing of donated blood

- Improved access to safe blood

- Training of health personnel.

The measures for preventing sexual transmission of HCV infection include:

- Promotion of correct and consistent condom use

- Routine testing of sex workers in high-prevalence settings

- Integrated action to eliminate discrimination and gender violence, and increased access to medical and social services for vulnerable persons such as intravenous drug users, commertial sex workers and patients with HIV. [38]

Public Health Action component in terms of planned response is an undividable and important part of the conceptual framework.[43] We propose three actions to reduce and prevent the spread of the infection.

3.2.6.1 Treatment as strategy of prevention

Treating infected patients is one of the ways of preventing the distribution of the HCV. Treatment may reduce transmission and result in HCV prevalence reduction.[51,52] In order to get successfully treated with currently available medications people should have better access to DAA medications. The registration of DAA medications is an important step forward in the management of the Hepatitis C. The MOH can encourage pharmaceutical companies (the authorized representatives of the manufacturer of the medicinal products) to register DAA medications. The MOH in cooperation with "The scientific Centre of Drug and Medical Technology Expertise after academician E. Gabrielyan" CJSC, can include these medications in

the two lists: the first is the list of medicines recommended for registration by the Pharmacological Council of MOH of the Republic of Armenia.[53] The list is public and available for the local pharmaceutical companies and also other foreign manufacturers. The second one is "The list of life-needed low-demand medications ".[42]

This model of prevention shows that scaling up treatment for HCV could be critical for reducing the prevalence of HCV infection among people who inject drugs.[52,54–56] DAA therapy is likely to be acceptable to patients as it is shorter in duration, easier to administer, leads to higher cure rates, and leads to fewer adverse events. DAA requires lower health system expenses as compared with interferon-based treatment, because the treatment duration for the former is shorter.

The WHO suggests that "patients in low-income countries can benefit from low-cost generic formulations where licensing agreements have been signed with companies that manufacture generic medicines."[38] Some countries negotiate tiered prices directly with the manufacturers. Due to these price arrangements, the price of DAA therapy is lower than interferon-based therapy in countries such as Mongolia and Ukraine. [38]

3.2.6.2 Development of a national guideline for HCV management

Health-care providers often face difficult decisions and considerable uncertainty while treating patients. They rely on the scientific literature, in addition to their knowledge, skills, experience, and patient preferences, to make their decisions. Clinical guidelines give opportunity to have standardized actions based on the knowledge of experienced professionals and best available evidence at the time of completion.[57]

The latest Methodological guideline approved by MOH describes case detection, diagnosis and registration only. It does not contain information about the treatment strategies,

care and follow up screenings. The proposal suggests developing a national guideline which will contain whole necessary information for HCV management. The suggested guideline will conation recommendations for the healthcare professionals how they should deal with people with HCV infection. The objective of developing a national clinical guideline is to provide evidence- based recommendations covering all stages of the patient care pathway: screening, testing, diagnosis, referral, treatment, care and follow up of patients with, or exposed to hepatitis C virus (HCV) infection.

3.2.6.3 Educational programs and social ads

We propose to raise the awareness on prevention of HCV infection among vulnerable groups: mostly young people who can be drug users, who are doing tattoos, medical workers who deal with contaminated blood every day due to their work, and others. Non-Governmental Organizations (NGO) can be involved in raising awareness of the population. Raising awareness of the population can be done through campaigns, social ads and mass-media.

1.   "Get a tattoo and nothing more" can be the title of an educational poster posted in tattoo salons. The poster should contain general information about HCV and emphasize the vector of the infection.

2.   "Get a new nail design and nothing more" can be the title of an educational poster located in beauty salons (manicure and pedicure services). The poster should contain general information about HCV and emphasize the vector of the infection.

3.   The proposal suggests developing a leaflet with 4 major domains that contain information regarding HCV (risk groups, screening, treatment, governmental support). The leaflets are intended for being distributed among vulnerable groups of HCV (patients on dialysis,

intravenous drug users, commercial sex workers, health care workers, persons with HIV infection, prisoners and previously incarcerated persons).

4.   The employees of tattoo/piercing and beauty salons (tattoo-piercing and nail professionals) should be provided with leaflets containing information regarding HCV. The information in the leaflets should be somewhat different from the leaflets provided to vulnerable population groups. These leaflets should be more concentrated on the transmission pathways.

5.   "Harm reduction" is a range of public health policies designed to reduce the harmful consequences of the use of legal and illegal recreational drugs that may not result in reducing drug consumption.[58] Intravenous drug users should be provided with blueprint and a short guideline about safe injection. The guideline should contain information about needle and syringe use, cooker distribution, filter distribution and tourniquet distribution.

6.   Non Governmental Organizations (NGO) in collaboration with government can organize charity photo exhibition called "After". The photo exhibition shows the complications in the life of patients with HCV (especially financial consequences of affording the treatment, when patients have to refuse themselves in order to save money for their treatment).

7.   The other component of the preventative measures is social ads with famous Armenian persons (politicians, scientists, sportsmen and representatives from show business). These celebrities should emphasize the positive sides of HCV-free life and motivate HCV patients for treatment. The social ads could be organized by the NGOs with the help of mass-media.

3.3 Evaluation plan synopsis

The evaluation of the proposed project will focus on the quality of the surveillance system. The quality of the surveillance system is defined by attributes such as completeness,

timeliness, usefulness, sensitivity, positive predictive value (PPV), specificity, accessibility, representativeness, simplicity, flexibility, acceptability, and reliability.[59]

The proposal suggests evaluating the quality of data registered in the surveillance system (completeness and validity), checking the HCV treatment coverage and doing economic evaluation of the intervention (cost-effectiveness analysis). The proposed evaluation will begin five years after establishing the surveillance system by the MOH (Department of Public Health).

Data quality is usually defined with two main attributes such as the completeness and validity of the data recorded in a public health surveillance system.[59–61]

3.3.1 Completeness

Completeness is the proportion of complete data fields or values within a dataset.[62] The proposal suggests to do annual assessment of completeness of the database after establishing the surveillance system. The assessment should be implemented by the MOH (Department of Public Health).

3.3.1.1 Completeness of case registration

Completeness of case registration refers to the match between the number of cases registered and the actual number of cases. This can be obtained by comparing the number of recorded HCV cases and reported to the next higher level over a period of time (a month) with the number of cases recorded in the patient register over the same period of time.[59] Evaluation can be conducted after one year of the project implementation.[61]

3.3.1.2 Completeness of the surveillance data

Completeness of the surveillance data is the match between the expected minimum data requirement and what is reported.[59] This can be obtained by comparing the number of the

recorded required HCV cases' characteristics over a period of time (a month) with the number of

actually recorded characteristics of cases recorded in the database over the same period of time.[59]

Evaluation can be conducted after one year of the project implementation.[61]

3.3.2 Validity

In the context of surveillance, validity describes the ability to capture the 'true value' of

the disease burden, such as incidence or prevalence.[45,62] Assessment of validity will be done by

comparing notified incidence rate (rate of notified cases using the population as denominator)

with expected rate in the same population based on previous reports.[62] The proposal suggests

annual assessment of the validity after establishing the surveillance system by the MOH

(Department of Public Health).

3.3.3 Treatment coverage

Treatment coverage is one of the ways of assessing the accessibility of the treatment.[63–65]

The proposal suggests to calculate the percentage of patients with HCV and registered in the

database receiving HCV treatment in the scope of surveillance system among the estimated

number of patients with HCV and registered in the database. The proposal suggests checking the

treatment coverage annually five years after establishing the surveillance system by the MOH

(Department of Public Health).

3.3.4 Cost-evaluation Analysis

Cost evaluation analysis is used to guide choices on the allocation of public or societal

resources (human and financial).[66] Cost-evaluation analysis is a tool for objectively assessing

the value of medical strategies, by examining health benefits and costs (investments). The

measurement of financial costs is relatively straightforward. The costs are the expenses planned

for the implementation of the project.[67] The benefits of the project, however, can be more difficult to measure. In order to measure the cost-effectiveness of the proposed project, the tool will focus on one of the main final outcome measurements (effectiveness indicator): Disability Adjusted Life Years (DALY) .[67,68] DALY is the sum of the Years of Life Lost (YLL) due to premature mortality and Years of Lost due to Disability (YLD) us a result of being infected with HCV.[69] The YLL will be calculated by multiplying the number of deaths by the standard life expectancy at the age at which deaths occurs.[70] In Armenia, the average life expectancy for men is 72 and for women is 78.[71] To estimate YLD for HCV in a particular time period (five years), the proposal suggests to multiply the number of incident cases in that period by the average duration of the disease (25 years)[72] and a weight factor that reflects the severity of the disease on a scale from 0 (treated and cured) to 1 (dead).[69] The higher the value, the less desirable it is (lower life expectancy and/or higher degree of disability).

$$DALY = YLL + YLD \quad [69]$$

DALY- Disability Adjusted Life Years

YLL- Years of Life Lost

YLD- Years of Lost due to Disability

$$YLL = N * L \quad [69]$$

N-number of deaths

L- standard life expectancy at age of death in years

$$YLD = I * DW * L \quad [69]$$

I - number of incident cases

DW - disability weight

L- average duration of the disease (years)

The proposal suggests implementing a project with combination of different interventions. For this kind of projects literature usually suggest using cost-effectiveness analysis design and calculate the Incremental Cost-Effectiveness Ratio (ICER) of each intervention compared with the situation of "doing nothing" or staying with the current situation.[66,68,73]

$$ICER = \frac{C_1 - C_0}{B_1 - B_0} \quad [68]$$

ICER- Incremental Cost-Effectiveness Ratio

C_1-Cost of intervention (surveillance system)

C_0-Cost of current strategy

B_1-Beneffits of intervention (surveillance system) (DALY)

B_0- Benefits of current strategy (DALY)

The proposal expects to get as lower value as possible (less expenditure and/or more benefits).

4. Planning /Budget

The implementation of the project has two stages.

4.1 First stage

- Surveillance system staff hiring
- Software development/adaptation

- Training of software users

- Educational programs and social ads for vulnerable groups

- Screening tests of population groups at high risk

- Treatment of patients diagnosed with HCV

- Follow-up laboratory tests

Some expenses such as software development, training of software users, and development of educational programs are one-time expenses which require funding only once.

4.1.1 Surveillance system staff

The newly developed surveillance system will need

- Program manager/coordinator (the person in charge for the whole program)

- Database manager (the person in charge for the database)

- Epidemiologist (to analyze the results)

- Biostatistician (to analyze the results)

- Programmer (technical management of the software)

The budget for one year is estimated to be 46,770 US$.

4.1.2 Software development

The process of software development has three main steps: Domain definition (www.HCV.am), programming and testing. These three steps will take 3 months. The budget for software development is estimated to be 7,290 US$.

4.1.3 Training of software users

The budget of the trainings is estimated to be 7,110 US $.

4.1.4 Educational programs

Recourses for educational programs implementation

➢ *Staff*

• Designer (design of posters and leaflets)

• Two photographers (taking photos for photo exhibition "After")

• Ads director (social adds with famous Armenians)

➢ Technical

• Printing (500 copies of posters, 50 000 copy of leaflets and 6,000 guidelines for drug users)

• Office rent for 15 days (photo exhibition "After")

• Broadcasting of social ads (15 seconds 3 times a day)

The total budget for educational programs is estimated to be 29,240 US $.

4.1.5 Treatment of patients diagnosed with HCV

One of the proposed public health actions is treatment of the patients already diagnosed with HCV. The vast majority of the overall budget is allocated for the treatment. As mentioned above, the officially notified prevalence of HCV in Armenia is 3-5%. The budget is calculated for 3% of population (2,998,600)[58] which is 89,958 US$. The treatment costs are calculated based on the prices of available medications in the local market (interferon/ribavirin). Appendixes 11 shows the budget of treatment with two treatment strategies (interferon/ribavirin and DAA (price of Ukraine)). The budget in the proposal is calculated with treatment strategy interferon/ribavirin. The total budget of treatment of prevalent cases is 563,300,000 US$.

4.1.6 Follow-up laboratory tests

The total budget for the follow-up laboratory tests is 17,410,000 US$.

The timetable of the first year actions is presented in Appendix 12.

4.2 Second stage

- Detection of new cases

- Treatment of newly diagnosed cases

- Follow-up laboratory tests

4.2.1 Detection of new cases

This section of the budget includes the expenses for screening tests among high-risk population groups for timely detection of HCV infection and further follow-up of detected cases. The total budget of this component is estimated to be 1,434,400 US$.

4.2.2 Treatment of new cases

One of the important aspects of the proposed project is the treatment of newly diagnosed HCV patients. The treatment costs are calculated based on the prices of available medications in the local market (interferon/ribavirin). Appendix 13 shows the budget of treatment with two treatment strategies (interferon/ribavirin and DAA (price of Ukraine)). The budget of the proposal is calculated with treatment strategy of interferon/ribavirin. The total budget of treatment is estimated to be 9,890,000 US$.

4.2.3 Follow-up laboratory test

The total budget for the follow-up laboratory tests is estimated to be 305,800 US$.

4.2.4 The overall budget

Budgeting of this project is based on personnel, operational and other project-related costs. The personnel salaries were calculated based on the rates of international and non-governmental organizations operating in the Armenian market. The budget consists of first-year expenses and the annual expenses after establishing the system. The total amount of the first year expenses is 581,136,000 US$ (Appendix 14) and additional 11,363,090 US$ (Appendix 15) for each year after establishing the surveillance system.

5. Ethical Considerations

The suggested evaluation plan fully satisfies the requirements of the Institutional Review Board (IRB) at the American University of Armenia.

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Appendix 1: Groups of people who should do mandatory Anti-HCV or Anti-HCV and HCV RNA test[10]

	Groups of people	Timeline	
		Anti HCV	Anti HCV and HCV RNA
1	Pregnant women	I and III trimester of pregnancy	-
2	Recipients of blood, blood components, organs and tissues	6 months after injecting blood or its components from people suspected to be infected with HCV	-
3	Donors of blood, blood components, organs and tissues	-	During each donation or taking each donor substance
4	Medical personnel and staff of service organizations. 1) Blood-centres 2) Departments of hemodialysis, organ transplantation and haematology 3) Clinical-diagnostic laboratories 4) Departments and cabinets of Surgery, Urology, Obstetrics and Gynaecology, Ophthalmology, Otorhinolaryngology, Anaesthesiology and Reanimatology, Stomatology, Infectious diseases, Gastroenterology (including medical dressing-rooms, intervention and vaccination cabinets) 5) Perinatal centres 6) Emergency departments and stations 7) Medical centres for disasters 8) Paramedical-Obstetric stations	Admission, following once each year (additional by instructions)	-
5	Patients from the departments of Hemodialysis, Kidney transplantation, Cardiovascular and Pulmonary surgery	During the admission, if it is requested by a physician based on clinical and epidemiological indications	30 days after addmitting and each month after that

6	Patients admitted for planned surgical interventions and before getting chemotherapy	During the admission or not less than 30 days before beginning treatment course	-
7	Patients with chronic diseases including liver diseases	During first clinical-diagnostic tests, additional by instructions	
8	Patients of Neurological and Dermatovenerologic dispensers, hospitalized patients besides Skin Fungal diseases and Scabies	During the registration and the next not frequent than once a year , additional by the instructions	-
9	Staff and participants of institutions where there are many children and old people (orphans, special schools, school internats, etc.)	Not frequent than once a year, additional by the instructions	-
10	People living in the centers of chronic Hepatitis C having contact with chronic Hepatitis C sources	Not frequent than once a year, 6 months after divorce or recovery of chronic HCV patient	-
11	Persons in the risk group of being infected with HCV 1. Intravenous drug users and their sexual partners 2. Commercial sex workers and their sexual partners 3. Homosexual man 4. Heterosexuals	At the time when risk factors are detected	-
12	People in Penitentiary Institutions	During the admission to medical facility, following by instructions	-
13	Children up to 12 years old born from mothers infected with HCV	-	At the age 2, 6,12 months (if at the age of 2 months HCV RNA is negative)

14	Persons having a contact with acute HCV outbreaks	-	When detecting an outbreak and one more time after 30 days
15	Persons having a contact with chronic HCV outbreaks	-	When detecting an outbreak

Appendix 2: Natural progression of hepatitis C infection[22]

```
                    ┌─────────────────────┐
                    │ HCV infection       │
                    └─────────────────────┘
                              ↓
                    ┌─────────────────────┐
                    │ Acute infection     │
                    │ 5-25% with symptoms │
┌──────────────────────┐   ↙  ↓  ↘   ┌──────────────────────┐
│ Clearance of HCV RNA │            │ Fulminate hepatitis  │
│ 15-25%               │            │  Rare                │
└──────────────────────┘            └──────────────────────┘
                    ┌─────────────────────┐
                    │ Chronic infection   │
┌──────────────────────┐   ↙  ↓
│ Extrahepatic         │
│ manifestations       │
│ Uncommon             │
└──────────────────────┘
                    ┌─────────────────────┐
                    │ Chronic hepatitis   │
                    └─────────────────────┘
                              ↓
                    ┌─────────────────────┐
                    │ Cirrhosis           │
                    │ 10-20% over 20 years│
                    └─────────────────────┘
                              ↓
                    ┌─────────────────────┐
                    │ Liver cancer        │
                    └─────────────────────┘
                              ↓
                    ┌─────────────────────┐
                    │ Liver               │
                    │ transplantation/    │
                    │ Death               │
                    └─────────────────────┘
```
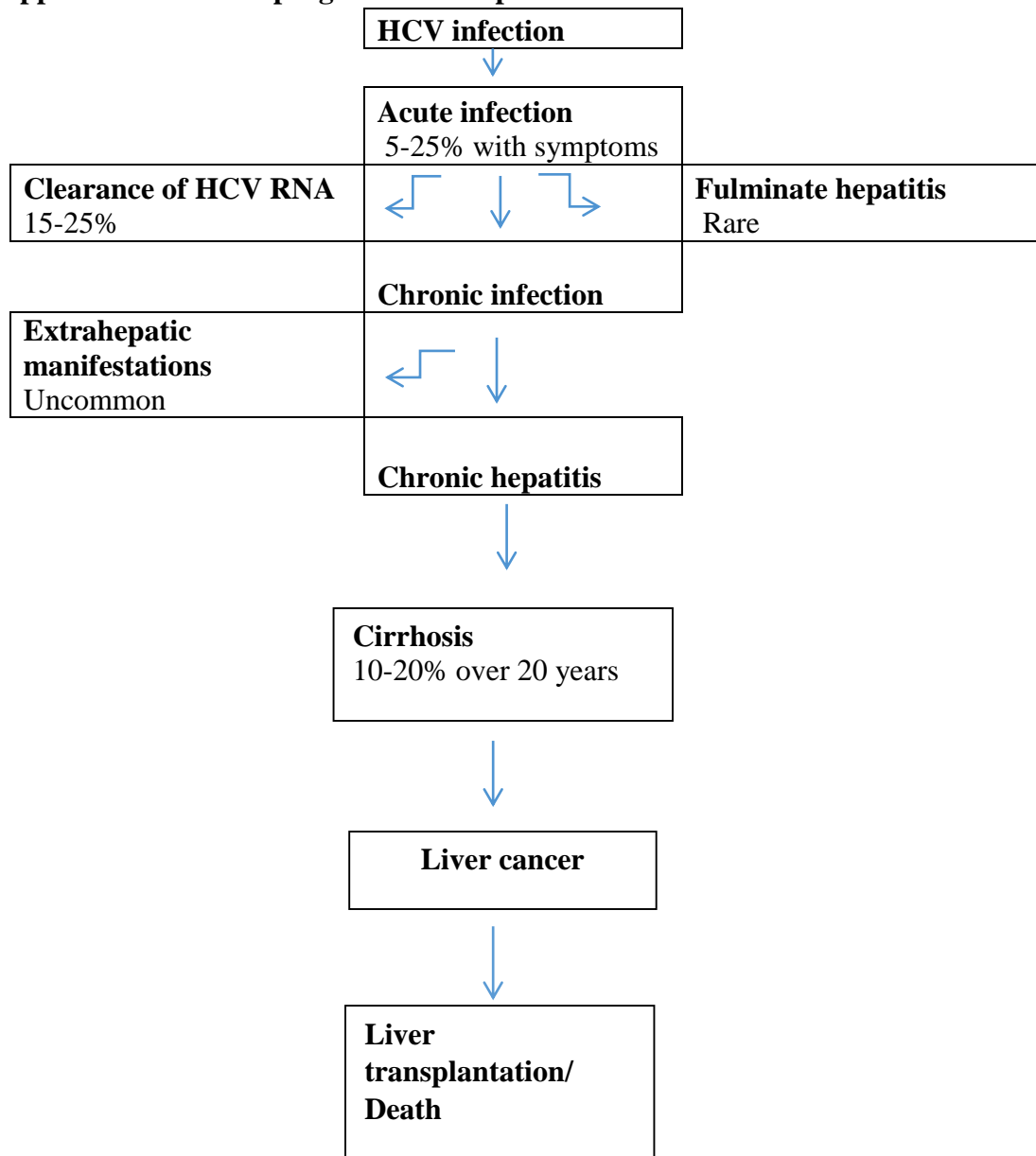
Appendix 3: Prices of HCV tests in the laboratories of Armenia (US $)[74–78]

Laboratories	Tests						
	Anti - HCV	PCR	ALT	AST	HCV RIBA	HCV RNA	HCV Genotype
A.B Med	12	102	3	3	-	20	102
EcoSense	12	102	3	3	408	-	102
Prom-Test	20	194	4	4	449	20	133
Cito-Lab	12	133	3	3	-	20	194
Dialab	14	82	2	2	-	20	-

Anti-HCV, Hepatitis C antibodies; PCR, Polymerase Chain Reaction; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase, HCV RIBA, Hepatitis C Virus Recombinant Immunoblot Assay; HCV RNA, Ribonucleic Acid of Hepatitis C Virus.

Appendix 4: Estimated cost of the treatment course per patient (CPP) and cost per sustained virologic response (CPSVR) of selected PEGylated interferon/ribavirin and DAA regimens in Brazil, Mongolia, and Ukraine (2015 US$)[38]

Countries	PEGylated interferon/ribavirin		DAA	
	CPP	CPSVR	CPP	CPSVR
Brazil	5368	10733	10831	11312
Mongolia	7036	15316	1709	1739
Ukraine	3173	6150	2953	3097

Appendix 5: Estimated total cost of treating all persons diagnosed with chronic HCV infection in Brazil, Mongolia, and Ukraine (2015 US$) with DAA regimens[38]

Countries	No. of persons with chronic HCV infection	No. of persons diagnosed	No. achieving SVR[i]	Drug cost	Other cost	Total cost
Brazil	2,036,570	314,934	299,734	3,324,524,994	65,984,876	3,390,509,821
Mongolia	198,764	59,629	58,249	81,417,808	19,897,906	101,315,714
Ukraine	1,024,858	410,783	387,365	972,405,729	227,160,446	1,199,566,175

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[i] Sustained Virologic Response

Appendix 6: Per patient price (for a treatment course) of HCV treatment medications available in Armenia (US $) [79–81]

Combination of drugs	AlfaPharm		Natali Pharm		Vaga Pharm	
	24 weeks	48 weeks	24 weeks	48 weeks	24 weeks	48 weeks
Rebetol 200mg + Pegasys 180mkg/0.5mg	-	-	6595	13189	-	-
Rebetol 200mg + Peginteron 150mg/0.5mg	-	-	7485	14970	-	-
Copegus 200mg +Pegasys 180mkg/0.5mg	4748	9495	-	-	4273	8546
Copegus 200mg +Peginteron 150mg/0.5mg	5638	11276	-	-	-	-

Appendix 7: Conceptual framework of public health surveillance and action[47]
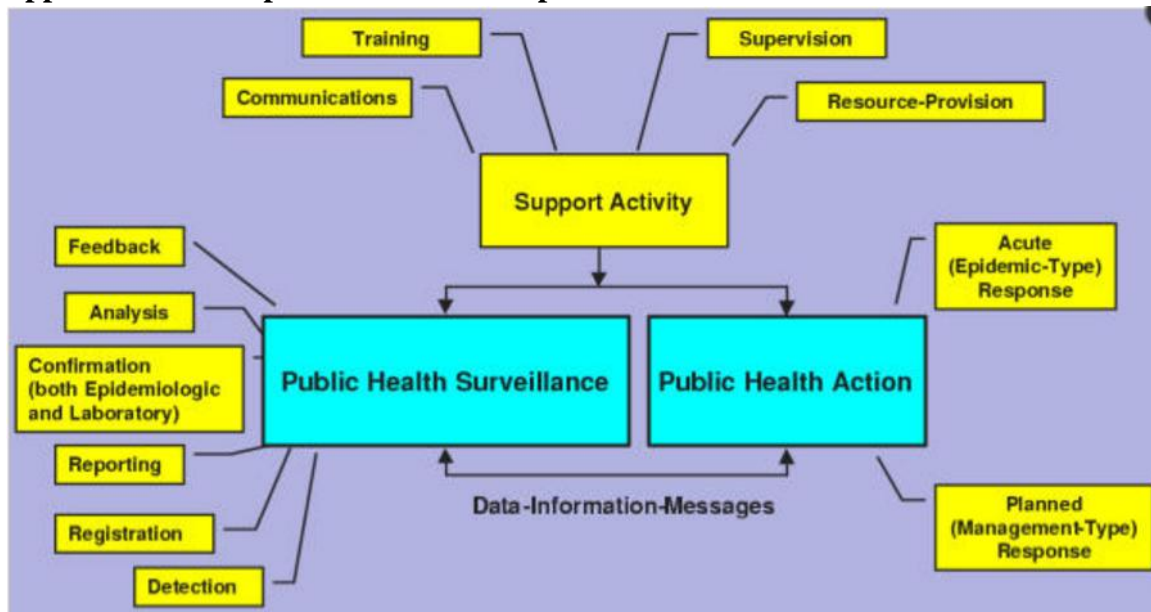
Appendix 8: The flowchart of case-reporting.[82]

| Detection and primary diagnosis of HCV | Case confirmation | Data recipients |

Policlinics

Hospitals

Laboratory for primary diagnosis

Clinical diagnosis

Laboratory diagnosis (case confirmation)

Database

National Center for Disease Control

Data management, analysis, reporting
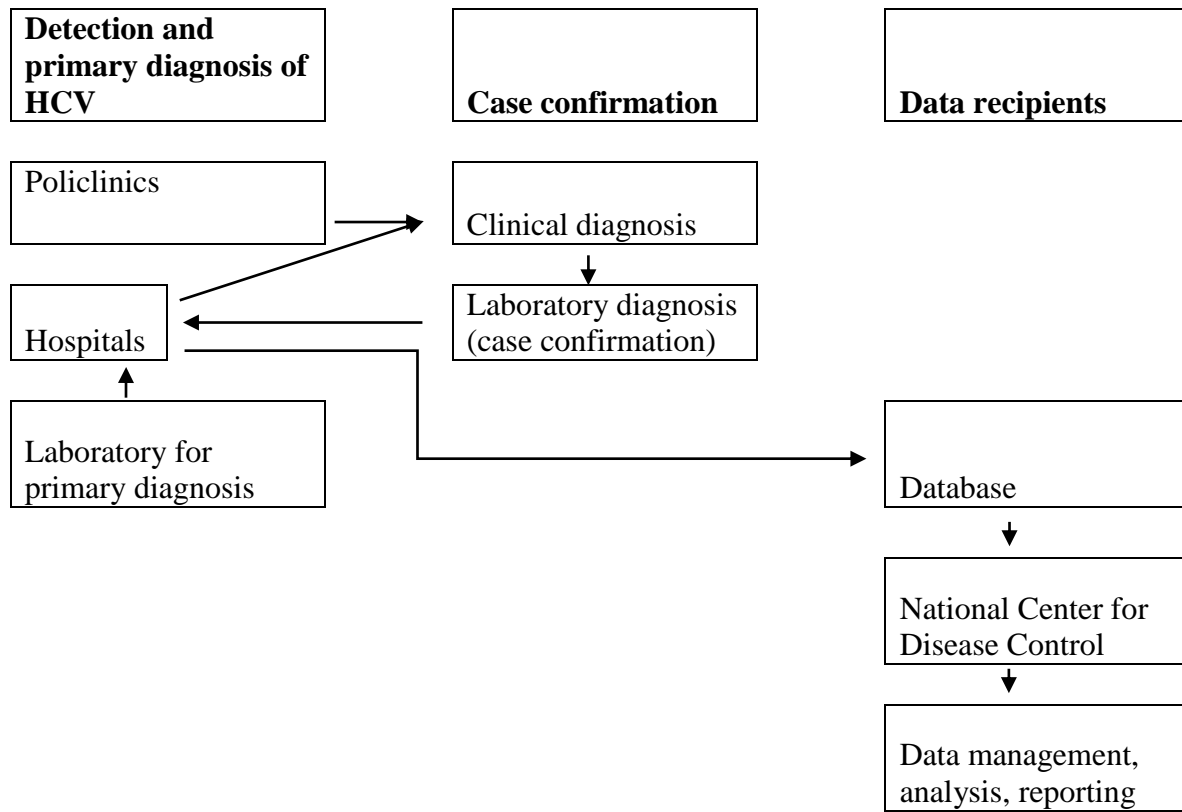
Appendix 9: Responsibilities of software users

Users	Responsibilities
Physicians (infectious disease specialists, hepatologists)	Online register a patient Enter the demographical characteristics of a patient Enter the medical history of a patient Enter the results of laboratory analysis of a patient Enter the strategies of treatment Enter the list of treatment medications Enter the side effects Monitor the dynamic of treatment Monitor the treatment outcome of a patients Analyze the information recorded in the software Develop standard reports (from data of his/her patients) • incidence • prevalence • demographic characteristics • co-infections or co-morbidities rate • contamination origin (probable or established) • adverse effects • rate of treatment outcomes • treatment history • case management agenda (dates of analysis) Search information
Chief physicians of laboratories	Enter the results of laboratory analysis of a patient Search information
Monitoring and evaluation professionals of the National Centers of Disease Control	Monitor the dynamics of treatment Monitor the treatment outcome of patients Analyze the information recorded in the software Develop standard reports for each medical institution, for each city, for each Marz and the whole country • incidence • prevalence • demographic characteristics • co-infections or co-morbidities rate • contamination origin (probable or established) • adverse effects • rate of treatment outcomes • treatment history • treatment cost • case management agenda (dates of analysis) Monitor the HCV- treatment strategies and strategies in different cities of Armenia and the whole Republic Search information

Chief of Research institute of epidemiology, virology and medical parasitology named after A.B. Alexanian	Analyze the information recorded in the software Develop standard reports for each medical institution, for each city for each Marz and the whole country • incidence • prevalence • demographic characteristics • co-infections or co-morbidities rate • contamination origin (probable or established) • adverse effects • treatment outcomes • treatment history • case management agenda (dates of analysis) Monitor the HCV- treatment strategies and strategies in different cities of Armenia and the whole Republic Search information

Appendix 10: Schedule of trainings

Time	Activities
11:00-13:30	Introduction Entering Case-Information Group work 1 (practice the skills from the lecture) Entering Case –Information (results from laboratory analysis, medications) Group work 2 (practice the skills from the lecture)
13:31-13:59	Break
14:00-16:30	Development of standard reports Group work 3 (practice the skills from the lecture) Monitoring of the database Discussion " The benefits of HCV-manager"

Appendix 11: Budget of treatment (Interferon/ Ribavirin) of already identified cases with Interferon/ ribavirin and DAA (US$)

Genotype	Interferon/ribavirin			DAA		
	Price /per unit (person)	Quantity (at least)	Total	Price /per unit (person)	Quantity (at least)	Total
2.3	4,300	51,000	219,300,000	3,000	51,000	153,000,000
1.4	8,600	40,000	344,000,000	3,000	40,000	120,000,000
	Total		**563,300,000**			**273,000,000**

Appendix 12: Timetable for the first year

	Implementers	Actions	Budget	Time table (months)											
				1	2	3	4	5	6	7	8	9	10	11	12
1	Government/ IT company	Software development/adaptation	7,290	x	x	x	x								
2	Trainers	Training of software users	7,110				x	x							
3	Government	Surveillance stuff hiring	47,040	x	x	x	x	x	x	x	x	x	x	x	x
4	NGOs, Government	Educational programs	36,740					x	x	x	x				
5	Physicians/ Hospitals	Treatment of prevalent cases	563,300,000				x	x	x	x	x	x	x	x	x
6	Physicians/ Laboratories	Follow-up laboratory tests	17,410,000					x		x		x		x	
7	Physicians/ Laboratories	Screening tests of population at high risk	590,200							x	x	x			
8	Physicians/ Hospitals	Detection of new cases	538,400								x	x	x		
9	Physicians/ Hospitals	Treatment of new cases	9,890,000							x	x	x	x	x	x
10	Physicians/ Laboratories	Follow-up laboratory tests	305,800									x		x	x
11	NCDC of Armenia	Data analysis	-					x	x	x	x	x	x	x	x
12	MOH	Dissemination	-											x	x

Appendix 13: Budget of treatment of newly detected cases with Interferon/ ribavirin and DAA (US$)

Genotype	Interferon/ribavirin			DAA		
	Price /per unit (person)	**Quantity (at least)**	**Total**	**Price /per unit (person)**	**Quantity (at least)**	**Total**
2.3	4,300	900	3,870,000	3,000	900	2,700,000
1.4	8,600	700	6,020,000	3,000	700	2,100,000
	Total		**9,890,000**			**4,800,000**

Appendix 14: Budget for the first year (US$)

1	Software	Price /per unit (hour)	Quantity	Total
	Project coordinator	18	177	3,190
	Web developer	15	41	620
	Web designer	13	30	390
	System operator	15	75	1,130
	System quality assurance (testing)	10	31	310
		Price /per unit	**Quantity**	**Total**
	Software	210	1	210
	Hardware	390	1	390
		Price /per unit (month)	**Quantity**	**Total**
	Database user license	12	12	150
	Domain (www.HCV.am)	40	12	480
	Hosting	35	12	420
	Subtotal			**7,290**
2	**Training**	**Price /per unit (day)**	**Quantity**	**Total**
	Office rent (2 days in each Marz and for 4 days in Yerevan)	30	24	720
	Transportation for two trainers (in Marzes)	10	40	400
	Transportation for physicians and laboratory workers from Marzes	6	40	240
	Hotel (2 trainers)	45	40	1,800
	Refreshments during the trainings (coffee/tea, cookies)	25	14	350
	Computers	600	6	3,600
	Subtotal			**7,110**

3	Staff	Price /per unit (person)	Quantity	Total (per month)	Total (per one year)
	Program manager	820	1	820	9,840
	Database manager	400	1	400	4,800
	Public health manager	750	1	750	9,000
	Epidemiologist	400	1	400	4,800
	Biostatistician	400	1	400	4,800
	Programmer	450	1	450	5,400
	Software trainer	350	2	700	8,400
	Subtotal			**47,040**	
4	**Treatment with Interferon/ribavirin (prevalent cases)**	Price /per unit (person)	Quantity (at least)	Total (per one year)	
	Genotype 2.3 (24 weeks)	4,300	51,000	219,300,000	
	Genotype 1.4 (48 weeks)	8,600	40,000	344,000,000	
	Subtotal			**563,300,000**	
5	**Follow-up laboratory tests**	Price /per unit (patient)	Quantity (at least)	Total (per one year)	
	Genotype 2.3 (24 weeks)	150	51,000	7,650,000	
	Genotype 1.4 (48 weeks)	244	40,000	9,760,000	
	Subtotal			**17,410,000**	
6	**Educational programs**				
	Staff	Price /per unit (month)	Quantity	Total	
	Designer	600	1	600	
	Photographers (2)	820	1	820	
	Ads director	750	1	750	
	Technical	Price /per unit (month)	Quantity	Total	
	Office rent	1000	1	1000	
	Broadcasting (15 seconds)	1,020	12	12,240	
		Price /per unit (copy)	Quantity	Total	
	Printing A3 (poster)	0.3	500	150	
	Printing A4 (leaflet)	0.2	50,000	10,000	
	Printing A4 (guideline for drug users)	2	6,000	12,000	
	Subtotal			**36,740**	

7	Testing major risk groups	Price /per unit (Anti-HCV)	Quantity (at least)	Total
	Patients on dialysis	13	700	9,100
	Intravenous drug users	13	5,400	70,200
	Commercial sex workers	13	7,000	91,000
	Health care workers	13	32,300	419,900
	Subtotal			**590,200**
8	Detection of HCV cases	Price /per unit (test)	Quantity (at least)	Total
	HCV RNA	30	1,600	48,000
	Genotype	110	1,600	176,000
	ALT	2	1,600	3,200
	AST	2	1,600	3,200
	PCR	90	1,600	144,000
	RIBA	410	400	164,000
	Subtotal			**538,400**
9	Follow-up laboratory tests	Price /per unit (patient)	Quantity (at least)	Total (per one year)
	Genotype 2.3 (24 weeks)	150	900	135,000
	Genotype 1.4 (48 weeks)	244	700	170,800
	Subtotal			**305,800**
10	Treatment with Interferon/ribavirin (new cases)	Price /per unit (person)	Quantity (at least)	Total
	Genotype 2.3 (24 weeks)	4,300	900	3,870,000
	Genotype 1.4 (48 weeks)	8,600	700	6,020,000
	Subtotal			**9,890,000**
	Total			**592,132,310**

Appendix 15: Budget (per one year starting from the second year)

1	Staff	Price /per unit (person)	Quantity	Total (per one month)	Quantity	Total (per one year)
	Program manager	820	1	820	12	9,840
	Database manager	400	1	400	12	4,800
	Public health manager	750	1	750	12	9,000
	Epidemiologist	400	1	400	12	4,800
	Biostatistician	400	1	400	12	4,800
	Programmer	450	1	450	12	5,400
	Subtotal					**38,640**

2	Software	Price /per unit (month)	Quantity	Total (per one year)		
	Database user license	12	12	~150		
	Domain (www.HCV.am)	40	12	480		
	Hosting	35	12	420		
	Subtotal			**1,050**		

3	Testing major risk groups	Price /per unit (Anti-HCV)	Quantity (at least)	Total (per one year)		
	Patients on dialysis	13	700	9,100		
	Intravenous drug users	13	5,400	70,200		
	Commercial sex workers	13	7,000	91,000		
	Health care workers	13	32,300	419,900		
	Subtotal			**590,200**		

4	Detection of HCV cases	Price /per unit (test)	Quantity (at least)	Total (per one year)
	HCV RNA	30	1,600	48,000
	Genotype	110	1,600	176,000
	ALT	2	1,600	3,200
	AST	2	1,600	3,200
	PCR	90	1,600	144,000
	RIBA	410	400	164,000
	Subtotal			**537,400**
5	Follow-up laboratory tests	Price /per unit (patient)	Quantity (at least)	Total (per one year)
	Genotype 2.3 (24 weeks)	150	900	135,000
	Genotype 1.4 (48 weeks)	244	700	170,800
	Subtotal			**305,800**
6	Treatment with Interferon/ribavirin (new cases)	Price /per unit (person)	Quantity (at least)	Total (per one year)
	Genotype 2.3	4,300	900	3,870,000
	Genotype 1.4	8,600	700	6,020,000
	Subtotal			**9,890,000**
	Total			**11,363,090**