



## Strategic Research Agenda: Health Research Priorities for Croatia

prepared for the project  
“The Information Office of the Steering Platform on Research for the Western  
Balkan Countries”

February 2009

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## 1. Purpose of strategic research agenda for Health

A key objective of the document is to provide an overview of the health research field in Croatia with a SWOT analysis of the health research capacities and identification of health research priorities for Croatia for 2009-2013. This report is based on consultations with researchers in health and other stakeholders in health research in Croatia and provides the basis of for developing the future EU-Western Balkan research co-operation within the framework of relevant EC research policies and funding programmes, including Framework Programme 7 (FP7).

The consultation process took place in February 2009 and provided the main input to the final report. A set of questions from the “Questionnaire for preparation of the national background report” was put forward to different groups of stakeholders in health research, including:

1. national health research policy makers (representatives from the Ministry of Science, Education and Sports (MSES), Ministry of Health and Social Care (MHSC), and other national authorities responsible for health research policy;
2. health research actors: research organizations from all sectors (public – academic and non-profit, and private), research hospitals, principal investigators of research grants;
3. industrial health sector: pharmaceutical and medical technology developers
4. beneficiaries of health research: patient organizations, individual users of health care system.

As the consultation process had a limited time frame, there was no public consultation but the questions were put forward to 20 experts. Their answers were followed by discussion in face to case or telephone interviews to identify research priorities in health. The priorities identified by individual experts were entered into a matrix and collapsed according to their frequencies and rank in individual lists. Specific research areas were then identified on the basis of expert opinions. During the consultation time-frame, 15 responses were collected, mainly from principal investigators of research grants. They came from 8 institutions from 4 cities, and from the private sector and patient representatives:

- School of Medicine, University of Zagreb 3 experts
- School of Medicine, University of Split 2 experts
- School of Medicine, University of Split (Croatian branch of Cochrane Organization) 1 expert
- School of Medicine, University of Rijeka 1 expert
- School of Medicine, University of Osijek 2 experts
- Sisters of Mercy University Hospital, Zagreb 2 experts
- University of Split Hospital Centre, Split 1 expert
- Agency for Quality and Accreditation in Health 1 expert
- Small/medium enterprise (SME) 1 expert
- Patient organization 1 expert

Because open consultations could not be performed, the research priorities in health outlined in this document are preliminary. Formulation of the final set of research priorities should be identified after a wider public consultation process, which would include a greater representation of all stakeholders in health research.

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the project leader of the research programme financed by the MSES on molecular interactions of body systems in health and disease. She also leads the IT project on creating the Croatian national register of clinical trials, and has established the Croatian Branch of the Cochrane Collaboration on evidence-based medicine. She has been the principal investigator of USA-Croatian research grant and Wellcome Trust grant in biomedicine. She is also a consultant for the World Health Organization, and past-president of the World Association of Medical Journal Editors and Council of Science Editors.

## **2. Health research environment in Croatia**

Health research environment in Croatia is primary influenced by the policies developed by the Ministry of Science, Education and Sports (MSES), which is also the largest funding body for all research in Croatia, including health research. However, some policy issues relevant for health research are provided in the documents developed by the Ministry of Health and Social Security, which primarily focuses on health care system and health insurance. This section will present the overall policy framework relevant for health research in Croatia and present the main elements of research policy making relevant for health research.

### **2.1 Croatian health research policy framework**

#### **2.1.1 The overall policy framework**

Although there is no separate policy specific for health, general policy documents adopted by the Government of the Republic of Croatia address issues relevant for health research. The most important document is the “Science and Technology Policy of the Republic of Croatia, 2006-2010” adopted in 2006 (available at <http://public.mzos.hr/fgs.axd?id=14189>).

The key objectives of this strategy, aimed at stimulation of scientific excellence and transfer of knowledge research results to industry and business to increase competitiveness and generate sustainable growth and productivity, are:

1. Increase funding for high quality research to meet the “3% of GDP for research investment” as laid out in the Lisbon Strategy set by the European Commission with goals to promote economic growth and job creation,
2. Restructure publicly-funded research institutes and R&D centres to reorient their research towards national priority areas and industry needs,
3. Encourage research partnerships and strengthen support schemes for young researchers - in order to facilitate mobility, interdisciplinary and cross-sector cooperation, and build a more flexible research and education system,
4. Invest in science research infrastructure and knowledge transfer institutions in order to build research capacity and provide access to business solutions,
5. Introduce measures to promote commercialization of academic research in order to encourage universities and research institutions to work more closely and effectively with business,
6. Introduce measures to promote technological development and innovation in order to attract people and capital into innovative business ventures, and
7. Administer stimulating and business-friendly legislation, including appropriate intellectual property laws and tax incentives for investment into priority area R&D, in order to build a system that encourages innovation.

All these objectives are relevant for health research area, as it is one of the fastest growing and most productive research areas in Croatia and in the EU. Specifically, one of the research areas recognized as perspective areas for Croatia and enabling the globalisation of knowledge, science and economic development is biotechnology. The Government of Croatia has set the goal to identify, stimulate and develop highly-specialized niches in biotechnology, so that it can become recognized in the global society and world economy.

Following the “Science and Technology Policy” from 2006, the Government of Croatia adopted the Action Plan 2007-2010 for identifying the policy priorities (Action Plan available at: <http://public.mzos.hr/lgs.axd?t=16&id=12955>). This Action Plan identified 9 long-term priorities, including health, in line with national interests and Framework Programs of the EU. Health was also among 4 short-term priorities, specifically the research related to food and agriculture, biotechnology, and social aspects of health.

To address the realization of the specific policy priorities, the following activities were proposed:

1. Establishment of the Council for National Innovation System, mandated with the activities related to the development of the National Innovation system,
2. Establishment of the Strategic Council for Science and Technology, as the highest policy body for the implementation of the Action Plan,
3. Improvement of the legislative and regulatory framework for science and technology development,
4. Education of research and technology community for commercial use of research and development,
5. Increase financial support of the science-technological sector,
6. Improve innovation-based businesses,
7. Join the research and technology framework of the EU and global scientific communities,
8. Increase public understanding of science,
9. Strengthen research and development in industry.

Croatia established a number of new institutions or national bodies to address the implementation of the policy action targets.

In the health research field, clinical research has high importance because of its technological and innovative nature and potential, research in health is closely related to the functioning of the health care system in the country. This is the reason why the policies developed for health care systems in Croatia must be evaluated in the context of health research. Health care system and health insurance are under the regulation by the Ministry of Health and Social Security, which does not fund research and technology. However, the National Strategy of the Health Care Development 2006-2011, adopted by the Croatian Parliament in 2006 (available at: [http://narodne-novine.nn.hr/clanci/sluzbeni/2006\\_06\\_72\\_1719.html](http://narodne-novine.nn.hr/clanci/sluzbeni/2006_06_72_1719.html)), states that the main aims of the strategy are to improve the health care system so that it offers the population high-quality medical and health care based on the principle of medical practice base on evidence.

The Ministry of Health has established institutions and bodies to improve the conduct of clinical research, as well as introduced the legal framework for clinical research oversight.

## 2.1.2 Elements of health research policy making

Action Plan 2007-2010 for identifying the policy priorities identified 9 long-term priorities:

1. Basic knowledge-driven research,
2. Environment protection and economic development of karst regions: Adriatic sea, coast and islands,
3. Agriculture, biotechnology, food,
- 4. Health,**
5. Information and communication technology,
6. Nanoscience, new materials, building and new production processes,
7. Energy, alternative and renewable energy sources, traffic and safety,
8. Social and humanistic sciences, Croatian identity,
9. Social integration, learning and education, life-long learning.

The Action Plan also identified 4 short term priorities for Croatia:

1. Environment (Adriatic sea, coast and islands, karst regions),
2. Health (food, agriculture, biotechnology, social aspect of health),
3. Energy and materials (alternative and renewable energy sources, bio-nanomaterials),
4. Croatian identity (Croatian contribution to culture, religion, art and science, Croatian language).

There is no specific science and technology policy for health, but the Government of Croatia has established a number of agencies and national bodies with a mandate related to research and development in general, including health research.

**Table 1.** National agencies relevant for research in Health research sector and related to the activities of the Ministry of Science, Education and Sports (information from “Overview of Achievements 2004-2007”,MSES)

|  |   |
|--|---|
| <b>Agency for Science and Higher Education</b>     | Agency for Science and Higher Education was founded in 2004, with the task of evaluating the institutions and programmes within the science and higher education system. The Agency is in charge of setting up a national network for quality assurance in higher education and providing professional assistance to the National Science Council, National Higher Education Council and Council for Science and Higher Education Funding and the Committee for Ethics in Science and Higher Education. |
| <b>Croatian Standards Institute</b>                | The Croatian Standards Institute was founded in 2004, with the task of preparing and adopting Croatian standards and other documents from the field of standardization, as well as keeping a record and archiving Croatian standards.   |
| <b>Croatian Accreditation Agency</b>               | The Croatian Accreditation Agency (CAA) in 2004, and accredits testing and measurement laboratories, natural and legal persons authorised for certification of products, management systems and the staff, as well as those performing technical supervision or other similar jobs.   |
| <b>Croatian Institute of Technology – HIT Ltd.</b> | The Croatian Institute of Technology – HIT Ltd. Was founded in 2006, as the result of the need for reorganising and significantly expanding the scope of the former Institute for Technological Policy and Development. HIT’s vision is to become the leading institution in Croatia in charge of developing and implementing technology policy. HIT’s mission is to develop and implement the programmes and projects that will enable an efficient interaction between the science and                |

|   |  |
|---|--|
|   | research resources and other aspects of the socio-economic system, providing fertile ground for the advent of new technologies and innovations (new products, production processes and services) in accordance with the concepts of sustainable growth and competitiveness on the global market.   |
| <b>Business Innovation Centre of Croatia – BICRO Ltd.</b> | Business-Innovation Centre Croatia – BICRO Ltd. was established by the Croatian Government in 1998 in the interests of stimulating the transfer of technology and commercialization, especially in the areas of small and medium-sized entrepreneurships, as well as contributing to the creation and development in the area of stockholder’s equity (especially venture capital), and promoting the establishment and development of science and technology parks, centres and related institutions.   |
| <b>Agency for Adult Education</b>                         | The Agency for Adult Education (AAE) was founded in 2006, and is responsible for monitoring, developing and evaluating adult education. AEA supervises work of adult education institutions, carries out professional training for the employed in this system and evaluates implementation of programmes for adult education. Within AEA, the Centre for Mobility and EU Programmes has been established, which shall as of 2009 implement the Lifelong Learning Programme and the EU programme Youth in Action. The Centre for Mobility and EU Programmes, which operated as a part of the Agency for Adult Education, became an independent agency in 2007. |
| <b>State Intellectual Property Office</b>                 | The State Intellectual Property Office of the Republic of Croatia is the state administration body with responsibilities in the field of protection of intellectual property rights. The Office carries out procedures for granting industrial property rights and performs the accompanying professional and legislative activity. The Office also makes the provision of information and services in the field of intellectual property, the cooperation with other institutions for the enforcement of intellectual property rights and support of innovation activity, as well as the cooperation with economic and R&D entities                           |

**Table 2.** National expert bodies related to the health research sector (information from “Overview of Achievements 2004-2007”, MSES)

|  |   |
|--|---|
| <b>Technological Council</b>             | The Technological Council was appointed in 2005 and entrusted it with a professional and consulting role in the process of Croatian innovative technological system development and with the task of project approval and supervision within the TEST programme. The Technological Council proposes to the Minister the R&D fields of a special interest to Croatia and it steers the TEST projects towards those priorities. |
| <b>National Bologna Follow-Up Group</b>  | The National Bologna Follow-Up Group was appointed in 2004 as a body responsible for the promotion of the Bologna Process at the national level and its follow up at the European level, as well as for the management of the activities and projects aimed at the Bologna Process promotion in Croatia   |
| <b>National Higher Education Council</b> | The National Higher Education Council is an expert body dealing with the development and quality of the entire higher education system in Croatia.  |
| <b>National Science Council</b>          | The National Higher Education Council is an expert body dealing with the development and quality of scientific research and the entire science sector in Croatia.   |
| <b>Croatian Innovation</b>               | The Croatian Innovation System Council was appointed in 2005, and is  |

|   |  |
|---|--|
| <b>System Council</b>   | responsible for strategic issue of the development and investment in the Croatian innovation system and coordination of the supporting institutions and their international partners. With its suggestions the Council promotes innovation culture in Croatia and applies innovative projects for developmental causes.  |
| <b>Council for Scientific Work and Higher Education Funding</b> | The Council for Scientific Work and Higher Education Funding was founded in 2005 as an expert body advising the National Science Council and the National Higher Education Council. The Council proposes criteria for allocation of budget funds for scientific work and higher education, and also monitors, reports and gives opinion on the financing of the science and higher education system. |
| <b>Council for Ethics in Science and Higher Education</b>       | The Croatian Parliament established the Council for Ethics in Science and Higher Education in 2005, as an independent body whose task is to promote ethical norms and values in science, higher education, business relations, public relations, employment of modern technology and in environment protection.  |

The Ministry of Science, Education and Sports also provided support to activities specifically related to health and biotechnology research:

1. **Mediterranean Institute for Life Sciences**

In accordance with the Technical-Business Cooperation Contract, which the former government signed with the Mediterranean Institute for Life Sciences (MedILS) on 16 November 2003, the Ministry has finished restoring buildings in the residential-tourist complex “Vila Dalmacija” in Split. Total investment costs were € 4.41 million. Further, the Ministry put at the disposal of MedILS the donated equipment in the value of € 108,900 which had been in the possession of the Ministry on the premises of the “Vila Dalmacija” complex. The Agreement on Mutual Rights and Obligations between the Ministry, MedILS and the Town and the University of Split was signed in 2006.

2. **Membership in European Molecular Biology Laboratory**

Under the Decision of the Croatian Government reached on 24 May 2006 and the adoption of the Act on the Ratification of the Contract for the Foundation of the European Molecular Biology Laboratory in the Croatian Parliament on 2 June 2006, Croatia became a full member of the European Molecular Biology Laboratory (EMBL). Croatia is thus the 19th member of this prominent scientific organization and the only transition country among members. The membership in the EMBL gave Croatian scientists access to state of the art research equipment in five large research laboratories employing 1,300 people, and an opportunity to participate in EMBL programmes and projects.

The “Brain-Gain” programme of the Ministry of Science, Education and Sports to repatriate Croatian scientists living abroad, also significantly contributed to the development of health research capacities in Croatia. The Ministry’s Scientist Return Project has since 2004 encouraged the return of 62 Croatian scientists from abroad, 14 of them in the field of health research.

**Table 3.** Croatian repatriated researchers in the field of biomedicine and health, since 2004

| <b>Name of the expert</b> | <b>Institution of origin</b>                    | <b>Institution in Croatia</b>            |
|---------------------------|---|--|
| Prof. Ivica Grković       | University of Melbourne, Melbourne, Australia   | School of Medicine, University of Split  |
| Željko Jeričević          | Baylor College of Medicine, Houston, Texas, USA | School of Medicine, University of Rijeka |
| Biserka Mulac Jeričević   | Baylor College of Medicine,                     | School of Medicine, University of        |



|                      |  |   |
|----------------------|--|---|
|                      | Houston, Texas, USA  | Rijeka  |
| Zoran Bogdanović     | Albert Einstein College of Medicine & Jacobi Medical Centre, New York, USA | Dubrava University Hospital, Zagreb                 |
| Karmen Jurašin       | Faculty of Medicine, University of Basel, Switzerland                      | University of Split Hospital Center, Split          |
| Prof. Nada Bešenski  | MUSC, Charleston, South Caroline, USA                                      | School of Medicine, University of Split             |
| Prof. Vedran Deletis | D. St. Luke's Roosevelt Hospital, New York (NY); USA                       | School of Medicine, University of Split             |
| Rozi Andretić        | The Neurosciences Institute, California, USA                               | University of Rijeka                                |
| Prof. Dražen Zanchi, | Université Denis Diderot, Paris, France                                    | School of Medicine, University of Split             |
| Zvonimir Koporc      | Vienna General Hospital (AKH), Vienna, Austria                             | Ruđer Bošković Institute, Zagreb                    |
| Branimir Čatipović   | Veterans Administration Clinic, Mason City, Iowa, USA                      | School of Medicine, University of Split             |
| Marinko Dobec        | Medizinische Laboriem, Zürich, Switzerland                                 | School of Medicine, University of Split             |
| Lea Vojta            | Ludwig-Maximilians Universität München, Germany                            | School of Veterinary Medicine, University of Zagreb |
| Aleksandar Vojta     | Ludwig-Maximilians Universität München, Germany                            | School of Veterinary Medicine, University of Zagreb |

The Ministry of Health and Social Security (MHSS) has established a set of regulatory documents, bodies and institutions responsible for the conduct of clinical research trials. According to the overview of procedures for ethical review of protocols in Europe, conducted by the European Forum for Good Clinical Practice (EFGCP) the Croatia has well-functioning legal framework for the conduct of clinical trials, (The EFGCP Report on The Procedure for the Ethical Review of Protocols for Clinical Research Projects in Europe, Croatia, update: March 2008, available at: [http://www.efgcp.be/Downloads/EFGCPReportFiles/Flow%20Chart%20Croatia%20\(revised\)%2008-03-01.pdf](http://www.efgcp.be/Downloads/EFGCPReportFiles/Flow%20Chart%20Croatia%20(revised)%2008-03-01.pdf)).

The laws or regulations applying to an application for conducting a clinical trial in Croatia are: The Law 71/07 of 9 July 2007 – Law about drugs (Zakon o lijekovima («Narodne novine» br. 71/07), and by-law (or rule) 121/07 of 26 November 2007 about clinical trials and good clinical practice (Pravilnik o kliničkim ispitivanjima i dobroj kliničkoj praksi («Narodne novine», br. 121/07).

The latter sets out the procedure and good clinical practice of clinical trials of drugs and medical devices, including the structure and appointment of Central Ethics Committee, and translated guidelines „Note for Guidance on Good Clinical Practice“ (CPMP/ICH/135/95) and „Clinical Investigation of Medicinal Products in the Paediatric Population“ (CPMP/ICH/2711/99).

There is a single Ethics Committee at national level, named the Central Ethics Committee. It is an independent body, whose members are appointed by the Croatian Minister of Health. This is the only EC that is authorized to approve clinical trial protocol for the investigation of medicinal products. A

procedure for approval is regulated by rules by the Minister of Health. Local Ethics Committees exist in health facilities and medical universities, and review research that is outside the scope of the national Central Ethics Committee.

Although the Rule on clinical trials and good clinical practice mandates public posting of approved clinical trial protocols, there is currently no information about past or ongoing clinical trials in Croatia.

The MHSS also established the national Agency for Quality and Accreditation in Health care, with the mandate to promote quality in the health system by evidence-based assessment of equipment, therapeutic procedures, and medicinal products, and establishment of the accreditation system for hospitals. Table 4. presents the overview of budget allocations for R&D in 2008, relevant for health research. The budget does not specify allocations directly for health research.

**Table 4.** Funding for R&D relevant for Biomedicine and Health in the Croatian 2008 budget

| <b>Ministry of Science, Education and Sports</b>                      |                   |
|---|-------------------|
| <b>Activity</b>   | <b>Funds (€)*</b> |
| Capital investment and building in higher education institutions      | 33.634.491,73     |
| Accession to the EU   | 2.686.666,67      |
| Subscription to international scientific journals                     | 3.421.333,33      |
| Research programs and projects  | 60.161.766,80     |
| Program of research fellows (novices)                                 | 38.219.268,00     |
| Stipends and fellowships for young researchers                        | 689.636,53        |
| Stimulation of scientific excellence                                  | 733.333,33        |
| Croatian Institute for Technology - HIT DOO                           | 66.666,67         |
| Development of knowledge-based small and medium enterprises (SME)     | 1.920.000,00      |
| International scientific and technological cooperation                | 8.482.689,47      |
| Linking SME with academia in the field of health (SMES go health/FP6) | 13.333,33         |
| European research area in biotechnology, ERA-IB                       | 28.346,00         |
| Project of linking researchers in the region, WESTBALKAN+/EU FP6      | 13.333,33         |
|   |                   |
| <b>Ministry of Health and Social Security</b>                         |                   |
| <b>Activity</b>   | <b>Funds (€)</b>  |
| Support to medical meetings and associations                          | 62.846,53         |
| Agency for the Quality Control and Accreditation in Health System     | 400.000,00        |
| Improvement of the transplantation program                            | 157.116,13        |
| Coordination in the area of genetically modified organisms            | 87.985,07         |
| Institute for Telemedicine  | 563.594,00        |
| Infrastructure for telemedicine on Croatian islands                   | 560.410,27        |

Exchange rate: 1€=7,5 Kunas

Besides the Ministry of Science, Education and Sports, which is the main funder in the area of health research, other independent or state agencies also provide substantial funding for health research.

The National Foundation for Science, Higher Education and Technological Development ([www.nzz.hr](http://www.nzz.hr)) was established in 2001. In 2007, it granted a total of 12.634.847,00 kunas (1.684.646,27 €) to research projects, individual grants or awards (<http://www.nzz.hr/images/stories/nzz/documents/pub/gi2007.pdf>). So far, the National Foundation

has given 22 grants related to health research. Thus, the National Foundation plays an important role in transforming the science and technology system, through its programmes for strengthening international cooperation, education of scientists, supporting the “brain gain” and reforming higher education. New legislature on the National Foundation, which is currently discussed in the Croatian Parliament, will enlarge the funding capacity of the Foundation and entrust it with independent evaluation of research grants in Croatia.

Croatian Institute of Technology – HIT (<http://www.hit.hr>) provides support and guidance for national technological development, monitors and anticipates global technological trends, provides advice and support in the area of intellectual property protection and transfer of technologies. The Institute also supports Croatian participation in European programmes for research and development and promotes Croatian research and technological development internationally. It is mandated with conducting technology foresight exercise in Croatia. HIT also hosts the National Contact Points for the European Communities FP7. HIT currently funds 12 technology development projects (TEST projects) with a total of 5.037.600,00 kunas (€671.680,00). Out of these projects, 4 are from the field of health research.

Unity Through Knowledge Fund – UKF (<http://www.ukf.hr>) is the funding body created by the Ministry of Science, Education and Sports with the support from the World Bank. UKF finances collaborative research projects and knowledge-based business activities of expatriates and Croatian researchers, institutions and companies. In 2007 and 2008, it funded 17 collaboration projects, out of which 6 were related to health research. The UKF also funded a number of smaller mobility grants for young researchers.

Finally, the Business Innovation Centre of Croatia – BICRO (<https://www.bicro.hr>) funds innovative technology projects with the aim of increasing the competitiveness of Croatian small and medium size enterprises and creating other conditions necessary for the successful flow of knowledge between the scientific community and the business sector. So far, technology centres have been established in Split (<http://www.tcs.hr>), Osijek (<http://www.tera.hr>) and Rijeka ([http://www.ticri.hr/index\\_hr.htm](http://www.ticri.hr/index_hr.htm)). BICRO has awarded 13.500.000,00 Kunas (€1.800.000,00) for the development of the Technology-Innovation Park in Rijeka, where an important part of the activities is dedicated to molecular medicine and translation medicine.

As there is not specific breakdown of funds for research areas, a search of the official reports or information on the web-pages of these funding bodies was made to identify research funds awarded in the area of health research. Table 5 presents the overview of the funds, but is by no means comprehensive or accurate.

**Table 5.** Funds for health research from major funding bodies in Croatia, 2007-2008

| <b>Funding body</b>  | <b>Total amount in Kuna</b> | <b>Total amount in €</b> |
|--|-----------------------------|--------------------------|
| Ministry of Science, Education and Sports (research grants)  | 38.786.000,00               | 5.171.466,67             |
| National Foundation for Science, Higher Education and Technological Development of the Republic of Croatia | 5.883.417,00                | 784.455,60               |
| Croatian Institute of Technology   | 5.037.600,00                | 671.680,00               |
| Unity Through Knowledge Fund   | 11.000.000,00               | 1.466.666,67             |
| <b>Total</b>   | <b>40.592.483,67</b>        | <b>5.412.331,16</b>      |

Croatia also has other institutions as stakeholders in health research, but there is no information on their participation in funding this type of research.

The Croatian Academy of Sciences and Arts enjoys the status of the most respected scientific institution in Croatia. It has established a number of scientific councils or boards for different areas of research ([http://info.hazu.hr/znanstvena\\_vijeca](http://info.hazu.hr/znanstvena_vijeca)) but health research has not been addressed.

The Croatian Academy of Medical Sciences is society of elected scientists, dedicated to the promotion of medical sciences and the furthering of health (<http://www.amzh.hr/eng/index-eng.htm>). Except for awards to young researchers and publications related to health research, the Academy of Medical Sciences does not have research funding activity.

The contribution of the private sector to funding of health-related research is not known. The latest data from the official national statistics (available now for 2006; Statistical Annual Bulletin from 2008, Central Bureau of Statistics, <http://www.dzs.hr/>) show that the total expenditures for research and development in the field of biomedicine and health was €25.455.000,33, with the following breakdown for sectors: business sector – € 5.014.00,67 , government sector – € 7.128.00,27, non-profit sector – € 0,00, and higher education sector – € 13.312.000,40. With 52% share in all expenditures for biomedical and health research, the Croatian higher education sector is definitely the strongest performer of health research in Croatia.

Data on the human resources for health research are not fully known. The Science & Technology Policy of the Republic of Croatia 2006 – 2010, provides numbers of researchers for the whole Croatia (for 2006): 3,232 Masters of Science, 5,780 Doctors of Science and 1,982 other researchers. According to the data of the Central Bureau of Statistics, the numbers of researchers for the biomedicine and health research are presented in Table 6.

**Table 6.** Human resources for health research in 2006\*

| Statistical parameter  | 2006   |
|--|--------|
| Number of PhD students graduated                                 | 68†    |
| Total number of R&D personnel                                    | 2976   |
| Percentage of women in the total number of R&D personnel         | 1718   |
| Total number of employees on a Full-Time-Equivalent (FTE) basis  | 1410,9 |
| Total number of researchers                                      | 2473   |
| Percentage of women in the total number of researchers           | 52.1   |
| Total number of researchers on a FTE basis                       | 1144.3 |
| Number of researchers with Ph.D. degree or higher                | 1361   |
| Number of researchers with Ph.D. degree or higher on a FTE basis | 585.2  |

\* Annual Bulletin, Central Bureau of Statistics, <http://www.dzs.hr>.

† Number of PhD theses defended in biomedicine, according to data registered in the Croatian National Scientific Bibliography, at [http://bib.irb.hr/skupni\\_podaci?s=3](http://bib.irb.hr/skupni_podaci?s=3)

## 2.2 Overview of health research activities

This overview presents currently funded research projects in the area of health, major research topics addressed, and the infrastructure for health research. As official public documents from the funding

bodies do not provide detailed breakdown for different research fields, the overview presented here is by no means complete or all-inclusive.

### 2.2.1 Health research projects

The Ministry of Science, Education and Sports currently funds 569 project from the field of “Biomedicine and Health”. The majority of these projects are joined in greater collaborative programs, currently 66 for health research. Table 7 presents the areas of research and the funds allocated for these research topics. Veterinary research is traditionally funded through the health and not agricultural sector, so is presented here.

**Table 7.** Number of and funds for on-going projects in “Biomedicine and Health” from the Ministry of Science, Education and Sports\*

|  |                                 |
|--|---------------------------------|
| Number of projects                                     | 569                             |
| Number of programs                                     | 66                              |
| Total funds  | 38.786.000,00 Kn/ 5.171.466,67€ |
| Breakdown of funds according to the research area (€): |                                 |
| Scientific standards for use of medicinal products     | 278.800,00 (5,39%)              |
| Brain research   | 548.800,00 (10,61%)             |
| Tumour research  | 768.533,33 (14,86%)             |
| Human infective diseases                               | 411.333,33 (7,95%)              |
| Cardiovascular diseases                                | 234.800,00 (4,54%)              |
| Chronic diseases                                       | 721.200,00 (13,95%)             |
| Public health  | 709.333,33 (13,72%)             |
| Transplantation of genes and tissues                   | 368.000,00 (7,12%)              |
| Human reproduction                                     | 239.066,00 (4,62%)              |
| Dental research  | 281.333,33 (5,44%)              |
| Veterinary research                                    | 610.266,67 (11,80%)             |

\*Source: Ministry of Science, Education and Sports, Directorate for Science.

The key institutions performing research in health are primarily higher-education institution, university hospitals and several institutes:

- University of Zagreb School of Medicine
- University of Rijeka School of Medicine
- University of Split School of Medicine
- University of Osijek School of Medicine
- Ruđer Bošković Institute
- Institute for Medical Research and Occupational Health
- Institute for Anthropological Research
- Institute for Immunology
- Zagreb University Hospital Centre
- Split University Hospital Centre
- Rijeka University Hospital Centre
- Osijek University Hospital
- School of Veterinary Medicine

A few health-related projects have been granted to the Croatian Academy of Arts and Sciences. There are also some other providers of health related-research which have recently emerged. One of them is

the Croatian Branch of the Cochrane Collaboration, established at the School of Medicine, University of Split, within the activities of the Croatian Centre for Global Health. This organization provides education and research in evidence-based medicine and health care.

The extent of funding and research activity in health-research by the private sector is not fully known, as there is no reliable and detailed information on health-research in this sector. What is especially lacking is the existence of small and medium enterprises (SME) in health research. Among the SMEs currently existing in 3 technology and innovation centres in Croatia (in Rijeka, Split and Osijek) supported by the Ministry of Science, Education and Sports, there is only a single SME in health: Genos Ltd, specialized for DNA forensic research. There is also Genera Ltd, a private biotechnology company, but there is no data available on its research activity in the public domain.

The data on the research at the major private research institution at Pliva pharmaceutical company, now GlaxoSmithKline Research Centre, is not available, and it is not known how the recent change of ownership for Pliva will affect research activities.

Mediterranean Institute for Life Sciences (MedILS, <http://www.medils.hr>) is a private research institute, but with significant contribution of public funds. Several research projects at MedILS are funded by the UKF.

### 2.2.2 Key competencies in health research fields

Croatian research in the area of health addresses all research fields recognized by the Organisation for Economic Co-operation and Development (OECD) – science and technology classification in the Frascati Manual – MEDICAL AND HEALTH SCIENCES (Appendix I). The Ministry of Science, Education and Sports groups the funded projects into 11 categories (Table 8).

**Table 8.** Number of research project in “Biomedicine and Health” field, funded by the Ministry of Science, Education and Sports\*

| Research field   | No. of projects | Average funds per project ( |
|--|-----------------|-----------------------------|
| 3-01. Scientific standards for use of medicinal products | 36              | 7.744,44                    |
| 3-02. Brain research                                     | 68              | 8.070,58                    |
| 3-03 Tumour research                                     | 81              | 9.488,06                    |
| 3-04. Human infective diseases                           | 29              | 14.183,90                   |
| 3-05. Cardiovascular diseases                            | 30              | 7.826,66                    |
| 3-06. Chronic diseases                                   | 87              | 8.289,65                    |
| 3-07. Public health                                      | 86              | 8.248,062                   |
| 3-08. Transplantation of genes and tissues               | 37              | 9.945,94                    |
| 3-09. Human reproduction                                 | 23              | 10.394,17                   |
| 3-10. Dental research                                    | 35              | 8.038,09                    |
| 3-11. Veterinary research                                | 63              | 9.686,77                    |

\*Source: Z-projects, Ministry of Science, Education and Sports, <http://zprojekti.mzos.hr/page.aspx?pid=96&lid=1>

Although the number of grants is high and cover the wide area of health research, the average amount of funds per projects is quite low. Also, there is still not enough true collaboration among research

groups at the same institutions and different institutions. Collaboration with the private sector is negligent.

The Ministry of Health and Social Security does not fund research projects but has several programmes related to or involving health research (Table 8).

**Table 8.** Projects and programmes of the Ministry of Health and Social Security Related to health research

|  |
|--|
| National programme for the control of bacterial resistance to antibiotics 2009-2014  |
| National directive for the prevention, control, and treatment of infections caused by meticillin-resistant <i>Staphylococcus aureus</i> (MRSA)   |
| Programme of measures for population protection: Programme of protection against infectious diseases – disinfection, fumigation and deratization at the area of the Republic of Croatia, 2008-2013   |
| Action community programme in the area of public health, 2008-2013   |
| Program for sustainable health care system   |
| Prevention programs: <ul style="list-style-type: none"> <li>• National programme for the health care of individuals with diabetes</li> <li>• National programme for early colon cancer detection</li> <li>• National programme for early breast cancer detection</li> <li>• Improvement of measures against HIV/AIDS in Croatia</li> </ul> |
| Programme for improvement of health care: <ul style="list-style-type: none"> <li>• National transplantation programme</li> </ul>   |

Principal investigators of research grants from the Ministry of Science, education and sports are located at the Medical Schools at 4 universities – Zagreb, Rijeka, Split and Osijek. Each School has groups of research excellence with productive and internationally visible researchers.

At the Zagreb University School of Medicine, there is a large research group in the field of Neuroscience, located at the Croatian Institute for Brain Research (<http://www.hiim.hr>). The School’s Centre for Functional Genomics is currently implementing the capacity-building project for strengthening genomic research in South-Eastern Europe, within the framework of the FP7 REGPOT programme. Finally, the newly established Centre for Translational Medicine, led by a high-profile research group in regenerative medicine is already equipped with state of the art equipment for molecular medicine and is actively engaged in building the human infrastructure to link research at the Medical School and Zagreb University Hospital Centre.

At the Rijeka University School of Medicine, the Centre for Antibody Production is the site for excellence in proteomic research and its research group continues with high-level viral immunity research. The research group at the Department of Molecular Medicine and Biotechnology is involved in frontier research in ribosome biogenesis.

The University of Split School of Medicine and its newly established Croatian Centre for Global Health are pursuing international collaborative research program aimed at establishing the “The Croatian National Biobank,” based on three large resources: 1) “10,001 Dalmatians” genome-wide study of Croatian island isolates; 2) a hospital-based DNA bank with thousands of cases with most common complex diseases; and 3) a large cohort from general population to serve as a control sample. The Medical School in Split also has high-profile research groups in neuroscience, translational medicine, and sports physiology.

The Medical School at the University of Osijek is the smallest research centre, but has internationally recognized research group in glycoproteomics.

### 2.2.3 Health research infrastructure

The Ministry of Health, Education and Sports continually invests into maintaining and developing research infrastructure at institutions that are main performers of health research. The infrastructure for health research can be best assessed by the number, quality and distribution of modern research equipment. The Ministry of Science, Education and Sports maintains a database with capital investment in research equipment infrastructure. Table 9 presents the capital research equipment at institutions performing health research.

**Table 9.** Existing research equipment as a part of the physical research infrastructure, funded by the MSES, registered in the National register of research equipment (<http://www.mzos.hr/dbApp/pregled.aspx?appName=kapitalna>)\*

|  |   |
|--|---|
| <b>School of Medicine, Osijek:</b>   |   |
| <ul style="list-style-type: none"> <li>• Automated laser microbeam AX 200</li> <li>• Cryomicrotome</li> <li>• Multifunctional microtiter plate reader for luminescence, fluorescence and colorimetry</li> <li>• ABI PRISM 3130-Avant genetic analyzer</li> <li>• ABI PRISM 7000 Sequence Detection System</li> </ul>   | <ul style="list-style-type: none"> <li>• Bone densitometer</li> <li>• Motorized research microscope</li> <li>• ABI PRISM 310 genetic analyzer</li> <li>• Motorized fluorescent research microscope</li> <li>• Electron microscope</li> </ul>  |
| <b>School of Medicine, Rijeka:</b>   |   |
| <ul style="list-style-type: none"> <li>• Confocal laser-scanning microscope</li> <li>• Autoclave for IVC systems</li> <li>• Real Time PCR, Model 7300</li> <li>• Laser microdissector</li> <li>• Liquid chromatographer-mass spectrometer</li> <li>• Upgrade for confocal microscope</li> </ul>  | <ul style="list-style-type: none"> <li>• Phosphoimager</li> <li>• Liquid chromatographer</li> <li>• Calorimeter (DSC)</li> <li>• FACSCalibur flow cytometer</li> <li>• Inverted and fluorescent microscope</li> <li>• System for SPF maintenance of laboratory mice</li> </ul>  |
| <b>School of Medicine, Split:</b>  |   |
| <ul style="list-style-type: none"> <li>• Agilent 2100 bioanalyzer</li> <li>• AMIS 2000 medical mass spectrometer system</li> <li>• Vivid 3 expert</li> <li>• ABI PRISM 377DNA Sequencer</li> </ul>   | <ul style="list-style-type: none"> <li>• Confocal microscope</li> <li>• MF/X Ultramicrotome</li> <li>• Real time PCR</li> </ul>   |
| <b>School of Medicine, Zagreb:</b>   |   |
| <ul style="list-style-type: none"> <li>• Mass spectrometer</li> <li>• Upgrade for 3T NMR Siemens</li> <li>• Power-Tome</li> <li>• Ultracentrifuge</li> <li>• Electron microscope</li> <li>• Research microscope</li> <li>• Gas chromatographer</li> <li>• DNA analyzer</li> <li>• Steam sterilizer</li> <li>• Combined neurolucida</li> <li>• Flow cytometer HERMES</li> </ul> | <ul style="list-style-type: none"> <li>• NMR Elscint</li> <li>• Ultracentrifuge</li> <li>• Immunofluorescent microscope</li> <li>• Flow cytometer FACSCalibur</li> <li>• Centrifuge</li> <li>• DNA detection system</li> <li>• Laser-scanning microscope</li> <li>• Fluorescent inverted microscope</li> <li>• DNA chip analyzer AFYMETRIX</li> <li>• Ultrasound probe system</li> <li>• PCR LIGHTCYCLER</li> </ul> |



|   |   |
|---|---|
| <ul style="list-style-type: none"> <li>• Flow cytometer and cell sorter FACSAria</li> <li>• Spectrum GX FT IR and FT RAMAN spectrometer</li> </ul>  | <ul style="list-style-type: none"> <li>• Research microscope</li> <li>• Mechanical microdissector</li> <li>• Research microscope</li> </ul>   |
| <b>School of Dentistry, Zagreb:</b>   |   |
| <ul style="list-style-type: none"> <li>• Dental laser</li> </ul>  |   |
| <b>School of Veterinary Medicine, Zagreb:</b>   |   |
| <ul style="list-style-type: none"> <li>• Flow cytometer Coulter Epics XL</li> <li>• Real Time PCR</li> </ul>  |   |
| <b>University of Osijek Hospital:</b>   |   |
| <ul style="list-style-type: none"> <li>• Real Time PCR</li> </ul>   |   |
| <b>University of Split Hospital Centre:</b>   |   |
| <ul style="list-style-type: none"> <li>• ABI Genetic Analyzer</li> <li>• Acidobase and gas measuring equipment</li> <li>• Mobile ergospirometric system</li> </ul>  |   |
| <b>University of Zagreb Hospital Centre:</b>  |   |
| <ul style="list-style-type: none"> <li>• None recorded</li> </ul>   |   |
| <b>School of Pharmacy, Zagreb:</b>  |   |
| <ul style="list-style-type: none"> <li>• Real-time PCR system</li> <li>• Flow cytometer FC500 MPL</li> <li>• Stopped-flow spectrometer</li> <li>• Stopped-flow - Rapid Scan spectrofotometer (UV-Vis and fluorescence)</li> <li>• Zetasizer 3000HS with titrator</li> <li>• Milestone microwave MLS-1200 mega Digestion System</li> </ul>   | <ul style="list-style-type: none"> <li>• Ultracentrifuge</li> <li>• ABI Prism 310 Genetic Analyzer)</li> <li>• Ion-exchange chromatography at high pH</li> <li>• ELISA plate reader (</li> <li>• High pressure liquid chromatography</li> <li>• EPR - spectrometer ELEXSYS 500</li> </ul>   |
| <b>Croatian Veterinary Institute, Zagreb:</b>   |   |
| <ul style="list-style-type: none"> <li>• Multiplicator for bacterial identification and sensitivity tests</li> <li>• BIOMERIEUX diagnostic system</li> </ul>  |   |
| <b>Institute of Anthropology, Zagreb:</b>   |   |
| <ul style="list-style-type: none"> <li>• ABI PRISM 310 Genetic Analyzer</li> <li>• Real-Time PCR</li> </ul>   |   |
| <b>Institute for Medical Research, Zagreb:</b>  |   |
| <ul style="list-style-type: none"> <li>• Ionisation chamber</li> <li>• System for gamma-spectroscopy</li> <li>• Beta counter</li> <li>• Alfa spectrometer</li> <li>• Fluorescent microscope</li> <li>• Cyto Vision Master System</li> <li>• Personal Lab Allergy Iason</li> <li>• Ultrasound densitometer</li> <li>• Ultracentrifuge</li> <li>• Spectrofotometer UV/VIS</li> <li>• Atom absorption spectrometer</li> <li>• Atom absorption spectrometer</li> <li>• Ion chromatographer</li> </ul> | <ul style="list-style-type: none"> <li>• Gas chromatography (GC) with 3 detectors (FID, PID, ECD)</li> <li>• System for gas chromatography and mass spectroscopy (GC-MS)</li> <li>• Gas chromatography (GC) with 2 columns and detector (GC-ECD)</li> <li>• Gas chromatography (GC) with 2 columns and detector (GC-ECD)</li> <li>• Gas chromatography (GC) with 2 columns and detector (GC-ECD)</li> <li>• Gas chromatography with detector (GC-TSD)</li> <li>• Gas chromatography with detector (GC-ECD)</li> <li>• HPLC-DAD</li> <li>• System for gas chromatography and mass</li> </ul> |

|  |   |
|--|---|
| <ul style="list-style-type: none"> <li>• HPLC with fluorescence detector</li> <li>• BTEX analyzer Ansyco</li> <li>• HPLC with fluorescence detector</li> <li>• System for gas chromatography and mass spectroscopy (GC-MS)</li> <li>• Microwave extraction system</li> </ul> | <ul style="list-style-type: none"> <li>• spectroscopy (GC-MS)</li> <li>• Thermal/optic analyzer for carbonized aerosols</li> <li>• ABI Prism Systems 2720&amp;7500 for DNA detection and quantification</li> <li>• Spectrofotometer UV/VIS with stopped-flow</li> </ul> |
| <b>Institute of Immunology:</b>  |   |
| <ul style="list-style-type: none"> <li>• Flow cytometer LSRII</li> <li>• Ultracentrifuge Optima XL80</li> <li>• DNA automated sequencer ABI 3130</li> <li>• Flow cytometer FACSCalibur</li> </ul>  | <ul style="list-style-type: none"> <li>• HPLC Waters 600</li> <li>• System for digital image detection</li> <li>• Bioreactor BIOSTAT B</li> </ul>   |

\*Does not include capital equipment for research granted to major research institute in Croatia, Ruđer Bošković, as there is no information on which equipment is used for health research.

The data in the register are not complete, as the institutions do not enter the data in a timely fashion.

Capital equipment is awarded to principal investigators of grants in a competitive procedure, stimulating collaboration of more grants and establishment of centres of excellence. The funds for capital equipment in health research remain constant over the last few years, at about €1 million per year, or about 17-30% of the total expenditure for capital research equipment.

**Table 10.** Funds for capital research equipment granted for biomedical research by the Ministry of Science, Education and Sports, 2006-2008

| <b>2006</b>  |  | <b>Total funds (€):4.423.378,40</b>  |
|--|--|--------------------------------------|
| <b>Biomedical research: 1.437.818,40 (32,5% total)</b>   |  |                                      |
| Zagreb School of Pharmacy                                | Flow cytometer, spectroscopy, PCR              | 150.324,40                           |
| Inst. for Med. Res.                                      | Carbon analyzer                                | 29.460,00                            |
| Univ. Hosp. Split  | Ultracut                                       | 42.526,67                            |
| Med. School Split  | Microdissecting microscope                     | 144.455,73                           |
| Med. School Rijeka                                       | Confocal and laser microdissecting microscopes | 290.421,33                           |
| Med. School Split  | Real time PCR, laparoscopic equipment          | 67.582,00                            |
| Med. School Zagreb                                       | 3T NMR   | 546.731,33                           |
| Zagreb Nat. Math. School                                 | Laser microdissector                           | 166.316,93                           |
| <b>2007</b>  |  | <b>Total funds (€): 5.194.579,87</b> |
| <b>Biomedical research: 1.497.333,33 € (28,8% total)</b> |  |                                      |
| Zagreb School of Pharmacy                                | Elisa reader                                   | 33.333,33                            |
| Inst. for Med. Res.                                      | Ionic chromatography                           | 44.000,00                            |
| Med. School Rijeka                                       | Cell sorter                                    | 266.666,67                           |
| Med. School Zagreb                                       | Cell sorter                                    | 213.333,33                           |
| Med. School Split  | Field equipment for bio-measures in humans     | 40.000,00                            |
| Med. School Osijek                                       | Animal care equipment                          | 46.666,67                            |

|  |   |   |
|--|---|---|
| Univ. Hosp. Split                                      | Cell culture equipment                              | 26.666,67                               |
| Hosp. Infect. Dis.                                     | Analytical instruments                              | 26.666,67                               |
| Zagreb University Centre                               | Mass spectroscopy                                   | 800.000,00                              |
| <b>2008</b>  |   | <b>Total funds<br/>(€):5.250.848,24</b> |
| <b>Biomedical research: € 904.730,67 (17,2% total)</b> |   |   |
|  |   | 91.397,33 €                             |
| Inst. for Med. Res.                                    | UltraCLAVE microwave pressure system                | 40.000,00 €                             |
| Veterinary School                                      | Pulsed field electrophoresis                        | 133.333,33 €                            |
| Med. School Rijeka                                     | Equipment for SPF maintenance of laboratory animals | 246.666,67 €                            |
| Med. School Zagreb                                     | micro CT  | 25.333,33 €                             |
| Med. School Osijek                                     | Vacuum microwave tissue processor                   | 33.333,33 €                             |
| Univ. Hosp. Split                                      | Movable x-ray                                       | 25.333,33 €                             |
| Hosp. Infect. Dis.                                     | Tissue preparation processor                        | 42.666,67 €                             |
| Med. School Split                                      | Physiology and genomics research equipment          | 266.666,67 €                            |

The overview of the research infrastructure for health research assessed as the availability of up-to-date, technologically advanced equipment, shows that there is substantive input into research infrastructure. However, it is also obvious that the distribution of the capital equipment is concentrated in a few centres, which have the largest number of researchers. There is a lack of research infrastructure at main clinical research centres. For example, the largest clinical research institution, Zagreb University Hospital Centre does not have any capital equipment registered, and has not been awarded any fund for capital equipment in the last 3 years, while other clinical research hospitals have procured some capital equipment. The reason for the disproportion in equipment allocation between clinical research centres and medical schools is their close cooperation in research, where most of the research is performed and governed from medical schools.

The Ministry of Health and Social Security does not invest in research equipment, but there is an ongoing, large scale investment programme for diagnostic equipment, particularly for in vivo imaging, totalling almost 7 million Euros.

Croatian researchers also have free online access to relevant research literature via the Centre for Online Databases, maintained by the Croatian Academic Research Network, CARNet.

## 2.3 Key drivers of health research

The key drivers for health research come from the public sector, as illustrated by the indices presented in this report. The contribution of the private sector to the health research is not known, although it can be estimated that the investment of international pharmaceutical companies into clinical research trials for new drugs and other medicinal products is significant.

### 2.3.1 Main health sector trends in Croatia

According to the reports of the Croatian Chamber of Economy on the sector “Manufacture of chemicals, chemical products and rubber and plastic products” (<http://hgk.biznet.hr/hgk/fileovi/13804.pdf>), the expenditure for R&D in this sector has been constant over the last 3 years: €5.960.000,00 in 2004,

€4.359.000,00 in 2005, and €5.014.000,67 in 2006, representing 1.7%, 1,4% and 1,7% total expenditures for R&D, respectively.

Report from the Croatian Chamber of Economy also identified the largest players in the pharmaceutical sector:

- Pliva Hrvatska, with total revenue of €43.635.000,00 and 2718 employees in 2007,
- Belupo, with total revenue of €90.032 and 915 employees in 2007,
- Pliva Famaceutika, with total revenue of €47.798 and 67 employees in 2007,
- Jadran galenski laboratorij, with total revenue of €42.828 and 339 employees in 2007.

There were 44 original patent applications to the Croatian State Intellectual Property Office (Table 11); this number does not include recognition of patents approved outside of Croatia.

**Table 11.** Patent applications in 2007 for “preparations for medical, dental purposes” (out of 442 patent applications in 2007)

| Field of technology/ International patent classification | Preparations for medical, dental purposes/A 61 |
|--|--|
| Resident applicants:                                     | 24   |
| Non-resident applicants:                                 | 20   |
| Total:   | 44   |

Source: Annual Report 2007, State Intellectual Property Office of the Republic of Croatia, [http://www.dziv.hr/webcontent/file\\_library/izvori\\_inf/pdf/godisnje\\_izvjesce\\_2007.pdf](http://www.dziv.hr/webcontent/file_library/izvori_inf/pdf/godisnje_izvjesce_2007.pdf).

### 2.3.2 Main socio-economic challenges in Croatia

The main socioeconomic challenges described in the report on ICT research priorities Croatia are all relevant for the area of health research.

As the main performer of the health research in Croatia is the sector of higher education, all challenges to this sector in general will affect health research in particular. The main problem of the higher education is lack of stimulation for excellence, as well as drain of young individuals from research to the private or health care sector. Although young researchers moving to health sector may be involved in clinical trials, they lack incentives for research advancement. Higher education sector is, like other society sectors in Croatia, burdened by corruption and “scientific inbreeding” and nepotism.

All these issues have been addressed by the relevant agencies, including the continuation of the curriculum reform at Croatian universities, incentives for young researchers, external evaluation and accreditation of higher education research institutions. Although the policies, action plans and activities are well designed, the problem is how they will be implemented, as there is resistance to change based on excellence and meritocracy.

The special challenges for health research in Croatia are major changes in the pharmaceutical industry, both at the local level, with the change of ownership of the largest Croatian pharmaceutical firm Pliva, and at the global level.

Lack of SMEs in health research is another important challenge, which is at least in part related to administrative barriers for entering the market in Croatia. Technology and innovation centres may be the best solution for this sector, but need greater support and promotion in the research community.

The lack of transparency of clinical trials in Croatia has negative effects, both the on the economic level and at the level of policy making, as it is difficult to create policy and plan actions if there is no information of on the input and output in this area of research and economy. Although the national legislation requires public posting of the approved trial protocols, this measure has not yet been implemented, leaving both the patient community and policy-makers without important information on health issues in their country.

Over the past decades, much of that research has been supported mostly by international pharmaceutical industry that found a high rate of return on the investment. As a consequence, Croatian physicians and scientists are in command of significant experience that makes them highly competitive in investigator-initiated clinical research, but also in contract-based clinical research. However, the need for improvement in good clinical practice for effective and ethical conduct of clinical trials is another major challenge for Croatia. Due to legislative terminology, central approval of clinical trials exists only for drugs and other medicinal products, including medical devices, while all other clinical research is handled by local, institutional ethics committees which are usually not well trained and experienced in ethical issues surrounding clinical trials (reviewed in Borovecki A, Oreskovic S, ten Have H. Ethics and the structures of health care in the European countries in transition: hospital ethics committees in Croatia. *BMJ* 2005;331:227-9).

### 3. Integration of Croatia in the European health research environment

Croatia participates in EU research area mainly through the Framework Programme, according to the Agreement between the European Community and the Republic of Croatia on the General Principles for the Participation of the Republic of Croatia in Community Programmes. The 7th Framework Programme for Research and Technological Development is the EU's main instrument for funding research and technological development in Europe.

The proposed budget for the Health Theme is €6.1 billion over 7 years (2007-2013). Table 12 lists EU-FP7 priorities in health research.

**Table 12.** Priorities in the EU FP7 (Source: [http://cordis.europa.eu/fp7/health/abouthealth\\_en.html](http://cordis.europa.eu/fp7/health/abouthealth_en.html))

|  |
|--|
| <p><b>Biotechnology, generic tools and medical technologies for human health – producing knowledge that will be applied in the area of health and medicine:</b></p> <ul style="list-style-type: none"> <li>• High-throughput research: enhancing data generation, standardisation, acquisition &amp; analysis.</li> <li>• Detection, diagnosis and monitoring: with emphasis on non-invasive or minimally invasive approaches.</li> <li>• Prediction of suitability, safety and efficacy of therapies: develop and validate parameters, tools, methods and standards (mainly through the Innovative Medicines Initiative - IMI) and alternatives to animal testing.</li> <li>• Innovative therapeutic approaches and interventions: gene and cell therapy, regenerative medicine, immunotherapy and vaccines.</li> </ul> |
| <p><b>Translating research for human health – making sure that basic discoveries have practical benefits and improve the quality of life</b></p> <ul style="list-style-type: none"> <li>• Integration of biological data and processes: large-scale data gathering, systems biology.</li> <li>• Research on the brain and related diseases, human development and ageing.</li> <li>• Research on infectious diseases (antimicrobial drug resistance, HIV/AIDS, malaria and tuberculosis, emerging epidemics, neglected infectious diseases).</li> </ul>  |

|  |
|--|
| <ul style="list-style-type: none"> <li>• Research on major diseases: cancer, cardiovascular disease, diabetes/obesity, rare diseases, other chronic diseases including rheumatoid diseases, arthritis and musculoskeletal diseases.</li> </ul>   |
| <p><b>Optimising the delivery of healthcare to European citizens – ensuring that the results of biomedical research will ultimately reach the citizens:</b></p> <ul style="list-style-type: none"> <li>• Translation of clinical outcome into clinical practice: patient safety, better use of medicines, benchmarking, pharmacovigilance.</li> <li>• Quality, efficiency and solidarity of health care systems.</li> <li>• Enhanced health promotion and disease prevention.</li> </ul> |
| <p style="text-align: center;"><b>Cross-cutting issues:</b></p> <ul style="list-style-type: none"> <li>• Child health.</li> <li>• The health of ageing population.</li> <li>• Gender-related health issues.</li> </ul>   |

These themes are implemented through 3 types of funding schemes: 1) Collaborative projects, 2) Coordination and support actions; and 3) Networks of Excellence. Inclusion of 'high-tech' SMEs in most projects throughout the work programme is a priority of the Health theme. Also, international cooperation is an important aspect of FP7 and is an integral part of Theme 1 on Health Research.

Currently, there are 3 FP7 research projects awarded to Croatian researchers in health (Table 13).

**Table 13.** FP7 research projects awarded to Croatian researchers in health field , from CORDIS database

|                 |   |
|-----------------|---|
| CAPRI2010       | Title: The center for antibody production Rijeka: upgrading the central research and service infrastructure for the South Eastern Region of Europe<br>Research area: REGPOT-2008-1-01 Any research topic covered by the EC FP7 (EC/EP Decision No 1982/2006/EC of 18 December 2006, published in the Official Journal 30.12.2006 L 412)<br>Project start date: [2009-03-01] |
| EUROGLYCOARRAYS | Title: Development of carbohydrate array technology to systematically explore the functional role of glycans in healthy and diseased states<br>Research area: PEOPLE-2007-1-1-ITN Marie Curie Action: "Networks for Initial Training"<br>Project start date: [2008-09-01]   |
| INTEGERS        | Title: Integrating and strengthening genomic research in South-Eastern Europe<br>Research area: REGPOT-2007-1-01 All thematic priorities' domains of the FP7<br>Project start date: [2008-05-01]  |

Croatian health researchers participate in a number of non-EU collaborative projects, including those funded by the National Institutes of Health in the USA and Wellcome Trust in UK.

Croatia still has to adapt to the EU legislation concerning clinical trials. The major legislative documents in this area ([http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10\\_en.htm#chap5](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm#chap5)) are:

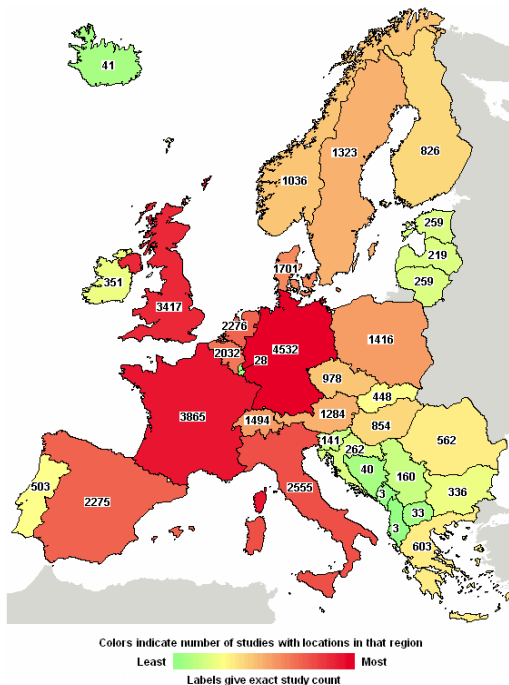
1. Directive 2001/20/EC OF the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use,

2. Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (Official Journal L 262, 14/10/2003 p. 22 - 26).
3. Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.

The legislation on clinical trials has been prepared by the DG Enterprise and Industry, but is closely related to research, especially with the recent requirement for public disclosure of data from clinical research trial protocols and trial results:

1. Guideline 2008/C168/02 on the data fields from the European clinical trials database (EudraCT) that may be included in the European database on Medicinal Products (July 2008),
2. Guideline 2009/C28/01 on the information concerning paediatric clinical trials to be entered into the EU Database on Clinical Trials (EudraCT) and on the information to be made public by the European Medicines Agency (EMA), in accordance with Article 41 of Regulation (EC) No 1901/2006 (February 2009).

Croatia has yet to fully conform to EU legislation in clinical trials. As the EudraCT database is at the moment closed to public, it is not possible to analyze clinical trials with sites in Croatia. At the moment, the only available data on clinical trials in Croatia is the register ClinicalTrials.gov of the National Library of Medicine in the USA, which the legislation makes mandatory and public registry for all clinical trials in the USA. Fig. 1 shows that ClinicalTrials.gov has 262 registered trials with the site in Croatia, including 83 open trials at the time of this report.



#### 4. SWOT analysis of health research capacity in Croatia

To analyze the current position of S&T in health research and explore future possibilities, SWOT analysis was used, as a technique often used to analyze a specific situation and develop suitable strategies and tactics, assess core competencies and capabilities, and provide evidence for change. SWOT stands for Strengths and Weaknesses (representing internal resources and capabilities), and Opportunities and Threats (representing factors external to the organization or group).

| <b>Strengths</b>  | <b>Weaknesses</b>  |
|---|--|
| <p>Critical mass of public and private institutions participating in health research</p> <p>Number of researchers with expertise in advanced research technology</p> <p>High-quality diagnostic equipment at university hospitals</p> <p>State of the art research equipment in the public sector</p> <p>Long-standing participation in international research programmes and collaboration with international scientific community</p> <p>Visibility of Croatian health researchers in international community</p> <p>Number of young researchers entering the field of health research</p> <p>Return of distinguished researchers from abroad</p>   | <p>Poor collaboration among research groups in the public sector</p> <p>Poor collaboration in health research between public and private sector</p> <p>Lack of transparency in the collaboration between private and public sector</p> <p>Large number of unused or little used capital research equipment</p> <p>Misbalance in high-level research infrastructure in Croatian regional centres</p> <p>Lack of project management skills</p> <p>Loss of young research fellows from research to non-research health care system</p> <p>Poor use of on-line resources and scientific literature</p> <p>Poor publication activity from degree level research</p> |
| <b>Opportunities</b>  | <b>Threats</b>   |
| <p>Health recognized as a high level national priority</p> <p>Expected increase in funding for research in general</p> <p>Versified public sector support for research and technological development in health</p> <p>Ongoing Croatian Technology Foresight program</p> <p>MSES program for return of international experts to Croatian science</p> <p>MSES funds for opening new research positions at universities and research institutions</p> <p>Full membership in FP7, ongoing accession to EU</p> <p>Ongoing health care system reform</p> <p>Existence of local scientific journals with international visibility (indexing in ISI databases)</p> <p>Access to current scientific literature via national Centre for On-line Databases</p> <p>Information and education service for intellectual property protection</p> | <p>No national health research priorities, especially in clinical research</p> <p>Unclear mechanism for implementing policies and strategies</p> <p>Misbalance in research funding and policies between the Ministry of Science and Ministry of Health</p> <p>No information on clinical research trials in Croatia</p> <p>Problems in the implementation of health care reform</p> <p>Few SMEs in health research, lack of cooperation with other sectors</p> <p>General brain-drain of researchers from Croatia</p> <p>Global and local financial crisis</p> <p>Lack of support for excellence in the higher education community</p>                         |



## 4.1 Strengths

The strengths of the health research in Croatia are in the size and experience of its researchers, and adequate infrastructure for health research, especially in the public sector.

A number of researchers in health area have also long-standing experience in participation in international research, and are experienced in competitive funding applications. They also have visibility in the international scientific community which is satisfactory for a small country with relatively low investment in research. In 2007, Croatian scientists from the field of biomedicine published 635 articles in journals indexed in Current Contents database of Thomson Reuters (source: Croatian National Scientific Bibliography, at [http://bib.irb.hr/skupni\\_podaci?s=3](http://bib.irb.hr/skupni_podaci?s=3)).

Health research also has relatively high number of young researchers entering the research system, as well as considerable return of experienced researchers from abroad.

## 4.2 Weaknesses

The weaknesses of the health research community is mainly in the lack of collaborative and focused actions, and poor use of capital equipment, coupled with redundancy in expensive and demanding equipment. The equipment is also not adequately distributed among main research performers in health.

The private sector does not contribute enough to the research efforts in this field, and there is a lack for SMEs in health, despite incentives offered by the national policies.

Croatian researchers, including those in health research, do not use on-line scientific information resources to their full extent, although access to these resources is available for free via CARNet.

One of the greatest problems in health research is the drain of young researchers from the research funding system. This drain of research fellows is common to all research fields, but is greatest in medicine, where only 12% of junior researchers obtained a degree of Doctor of Philosophy (PhD) before they terminated their fellowship to work outside of the research system in Croatia (Petrovecki M, Smiljanic L, Troselj M, Polasek O. Employment outcomes among junior researchers in medicine in Croatia. *Croat Med J.* 2008;49:91-7; Polasek O, Primorac D, Petrovecki M, Petrovecki M. Fellowship outcomes and factors associated with scientific successfulness of junior researchers in Croatia. *Drustvena istrazivanja* 2007;16: 1127-50). Also, the publication output at the degree level is not satisfactory, with only 14% of Master's and 34% of Ph.D. theses resulted in articles published in journals indexed in MEDLINE (Frkovic V, Skender T, Dojcinovic B, Bilic-Zulle L. Publishing scientific papers based on Master's and Ph.D. theses from a small scientific community: case study of Croatian medical schools. *Croat Med J.* 2003;44:107-11). These data indicate poor renewal capability of the health research community.

## 4.3 Opportunities

Health has been recognized as both a long- and short-term priority in the "Action Plan 2007-2010 for Science and Technology Policy of the Republic of Croatia", with expected increase in funding. Also, there is major restructuring of the grant support in Croatia, with greater emphasis on excellence in research. New opportunities for funding for health are available, both at the national level (from UKF, HIT and

BICRO) and international level (FP7 and other funds in and outside of Europe). This is facilitated by the full membership in the FP7 and closing negotiations of Croatia for full EU membership.

The ongoing Technology Foresight Program may open new opportunities for health research, especially for the development of SMEs in health.

The Ministry of Science, Education and Sports has put special emphasis and resources in developing human resources for research in general by opening new research position in higher education and research institutions, and by supporting return of experienced researchers from abroad.

The ongoing health reform provides opportunities for developing clinical research in Croatia, as well as the current efforts on increasing quality of health care and introducing evidence-based improvements in the health care system.

The Croatian government provides information and education support in the protection of intellectual property by the State Intellectual Property Office, as well as free on-line access to relevant scientific information. Finally, a number of Croatian scientific medical journals have become indexed in most prestigious bibliographical and citation databases such as Web of Science and Scopus, providing the opportunity for Croatian health researchers to present their work to the international scientific community.

#### **4.4 Threats**

Although health in general has been recognized as the national priority, specific research priorities within the large health area are not clear. This is especially true for clinical research, for which there is no clear policy and no transparency in the conduct of clinical trials. Misbalance and lack of coordination between the Ministry of Science and Ministry of Health in regulation and funding of clinical trial may further increase the confusion and promote poor quality research and poor clinical practices. The reform of the health care system is currently experiencing problems and delays, and this may take efforts away from priorities such as the implementation of EU directives for clinical research trials.

At the national level, many important policies and actions have been initiated to strengthen the research and development sector, but the mechanism for their implementation is not clear, especially in the context of resistance to reforms and stimulation of excellence in the scientific community.

Finally, the effects of global financial crisis on the Croatian economy threat to reduce the budget projections for research and development in the public sector, including the reduction of salaries. Such reduction would be a serious threat to already available opportunities for investment in research and development, particularly in regard to stimulating SMEs in health research.

### **5. Health research priorities for Croatia**

Research priorities outlined in this section have been identified on the basis of the consultation process, as well as the recently developed strategic research plans from three largest performers in medical research Medical Schools at the Universities of Zagreb, Rijeka and Split.

The consultation process and analysis of strategic research plans identified 3 themes:

1. Translational medicine,

2. Genetic and environmental determinants of health and disease,
3. Improving the quality of clinical research trials.

## **5.1 Translational medicine**

This aim combines two of the Fp7 priority health themes: “Translating research for human health” and “Biotechnology, generic tools and medical technologies for human health”.

Current research effort in Croatia aims to significantly contribute to translating basic discoveries into practical benefits and improvement of the quality of life.

Specific areas addressed within this strategic priority are:

1. Brain research and neurobiology of cognitive, mental and neurological diseases;
2. Research on complex, late-onset diseases, including cancer, cardiovascular disease, diabetes/obesity, and musculoskeletal diseases;
3. Human development and ageing;
4. Research on infectious diseases.

Croatia has already high-visibility research from these areas, and is building up the infrastructure and human resources for intensive translational research.

The important aspect of the four specific research priority areas is that they will be directed towards developing novel approaches to diagnosis and therapy, including:

1. Non-invasive or minimally invasive tools for detection, diagnosis and monitoring of diseases, and
2. Innovative therapeutic approaches, especially in regenerative medicine, immunotherapy and gene and cell therapy.

## **5.2 Genetic and environmental determinants of health and disease**

Croatia has already a strong research base for studying genetic and environmental determinants of health and disease, drawing from epidemiological research of isolated population on Adriatic islands. This effort is now an internationally recognized study “1001 Dalmatians” and the future goal to expand this sample is being carried out in the “10,001 Dalmatians” study.

The future specific aims for this research priority topic are:

1. Establishment of national Biobank for specific diseases, and
2. Integration of information from large-scale collections of biological data.

The Croatian National Biobank aims to collect the information from 4 different populations:

1. Genetically isolated populations from islands,
2. Patients with diseases of unknown aetiology and without preventable risk factors,

3. Patients with common complex diseases, which form the greatest share of the overall disease burden in the Croatian population, and
4. Individuals from general Croatian population.

The Biobank aims take into consideration 4 general levels of complexity involved in the development of human diseases: 1) genomics level; 2) “metabolomics” level (including proteomics, glycomics, and lipidomics); 3) level of intermediate quantitative traits (e.g., blood pressure, forced expiratory capacity, cholesterol levels, etc.); and 4) endpoint that results in a complex disease phenotype.

The development of the database is in line with the priorities from the two FP7 health themes, “Translating research for human health” and “Biotechnology, generic tools and medical technologies for human health”, specifically related to the specific aim of the “Biotechnology” theme – High-throughput research: enhancing data generation, standardisation, acquisition & analysis, and the specific aim of the Translational research” theme – Integration of biological data and processes: large-scale data gathering, systems biology.

### **5.3 Improving the quality of clinical research trials**

Developing translational research and biotechnology for human health is closely linked with the quality of clinical research. While the basic research in health is well developed and can be competitive in the EU research area, the legislative and organisational framework for clinical research, as well as the implementation of good clinical practice, is the primary strategic priority in order to ensure that basic discoveries have practical benefits for the patients and improve the quality of life.

Specific aims within the strategic priority of effective translation of basic discoveries to clinical research trials include:

1. Creation of database of approved clinical trials in Croatia,
2. Training of researchers in good clinical practice for clinical research trials,
3. Ensuring quality for care assessment of clinical research trial at the national level.

This strategic priority is in line with the FP7 Health theme “Optimising the delivery of healthcare to European citizens”

## Appendix I

Organisation for Economic Co-operation and Development (OECD)  
 Directorate for science, technology and industry, Committee for scientific and technological policy  
 27 February 2007

### Revised field of science and technology classification in the Frascati Manual – MEDICAL AND HEALTH SCIENCES

|            |   |
|------------|---|
| <b>3</b>   | <b>Medical and Health sciences</b>                                    |
| <b>3.1</b> | <b>Basic medicine</b>   |
| •          | Anatomy and morphology  |
|            | Human genetics  |
|            | Immunology  |
|            | Neurosciences (including psychophysiology)                            |
|            | Pharmacology and pharmacy   |
|            | Medicinal chemistry   |
|            | Toxicology  |
|            | Physiology (including cytology)                                       |
|            | Pathology   |
| <b>3.2</b> | <b>Clinical medicine</b>  |
| •          | Andrology   |
|            | Obstetrics and gynaecology  |
|            | Paediatrics   |
|            | Cardiac and Cardiovascular systems                                    |
|            | Peripheral vascular disease   |
|            | Hematology  |
|            | Respiratory systems   |
|            | Critical care medicine and Emergency medicine                         |
|            | Anaesthesiology   |
|            | Orthopaedics  |
|            | Surgery   |
|            | Radiology, nuclear medicine and medical imaging                       |
|            | Transplantation   |
|            | Dentistry, oral surgery and medicine                                  |
|            | Dermatology and venereal diseases                                     |
|            | Allergy   |
|            | Rheumatology  |
|            | Endocrinology and metabolism (including diabetes, hormones)           |
|            | Gastroenterology and hepatology                                       |
|            | Urology and nephrology  |
|            | Oncology  |
|            | Ophthalmology   |
|            | Otorhinolaryngology   |
|            | Psychiatry  |
|            | Clinical neurology  |
|            | Geriatrics and gerontology  |
|            | General and internal medicine   |
|            | Other clinical medicine subjects                                      |
|            | Integrative and complementary medicine (alternative practice systems) |

|            |   |
|------------|---|
| <b>3.3</b> | <b>Health sciences</b>  |
| •          | Health care sciences and services (including hospital administration, health care financing)  |
|            | Health policy and services  |
| •          | Nursing   |
|            | Nutrition   |
|            | Dietetics   |
| •          | Public and environmental health   |
|            | Tropical medicine   |
|            | Parasitology  |
|            | Infectious diseases   |
|            | Epidemiology  |
| •          | Occupational health   |
|            | Sport and fitness sciences  |
| •          | Social biomedical sciences (includes family planning, sexual health, psycho-oncology, political and social effects of biomedical research)  |
|            | Medical ethics  |
|            | Substance abuse   |
| <b>3.4</b> | <b>Medical biotechnology</b>  |
| •          | Health-related biotechnology;   |
|            | Technologies involving the manipulation of cells, tissues, organs or the whole organism (assisted reproduction)   |
|            | Technologies involving identifying the functioning of DNA, proteins and enzymes and how they influence the onset of disease and maintenance of well-being (gene-based diagnostics and therapeutic interventions (pharmacogenomics, gene-based therapeutics) |
|            | Biomaterials (as related to medical implants, devices, sensors)   |
|            | Medical biotechnology related ethics  |
| <b>3.5</b> | <b>Other medical sciences</b>   |
| •          | Forensic science  |
| •          | Other medical sciences  |

Available at <http://www.oecd.org/dataoecd/36/44/38235147.pdf>.