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REVIEW ARTICLE

The impact of the European financial crisis on clinical research within the European union or "when life gives you lemons, make lemonade"

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Abstract

The European Union (EU) and the world are faced with unprecedented economic challenges, which if allowed to persist could threaten its continued existence in its current form as a union. Furthermore, these same financial challenges can easily translate into societal hardship. The biomedical and pharmaceutical industries of the U.S. and Europe have been in the midst of severe financial constraints over the last few years, which will worsen in the coming years. A critical factor is a financial crisis that appears to be spreading like wildfire through Europe, with 3 of its oldest members (Greece, Ireland, Portugal) already having enlisted the aid of the International Monetary Fund (IMF) to avoid bankruptcy, and with the possibility of others to follow (Italy, Spain). Adding to this the increasing cost of introducing new medications and devices, and conducting clinical research, as well as the tightening regulatory pressures and the drying pharmaceutical pipelines, cost cutting pressures are mounting on pharmaceutical industries and the biomedical sector, whether in academia or in industry. This paper will attempt to highlight some of the problems that clinical research in Europe may be facing, as well as discuss some of the potential solutions. Although this will by no means be an exhaustive analysis, the goal is to show that times of financial hardship, such as the current one, may also provide the impetus for constructive change. Hippokratia. 2012; 16 (1): 6-10

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In order to approach the issue of conducting research at a time of financial crisis, this paper will list first some of the problems identified, as well as some confounding factors. This will be followed by describing some potential solutions, which all have as a basic tenet the cooperation between the different players involved, including members of the EU, private enterprise and academia. The guiding principle throughout all this is to be able to view clinical research and innovation not as burdens to the financial plans of the member states and the EU as a whole, but rather as the means to overcome today's challenges while promoting development and a more competitive EU in the world scene.

Problems identified/confounding factors:

European financial crisis*:* The financial crisis spilled over into a public finance crisis, as for example in the case of Greece and Portugal. The EU tried to respond to this challenge by establishing new procedures so that the crisis would neither speed up, nor would it happen again. The situation is unprecedented, because the European Central Bank (ECB) has not one, but 17 sovereigns. If the government bonds of some sovereigns are accepted by the ECB above their true market values, this can happen only at the expense of the other sovereigns. In order to avoid the problems this scenario creates, under the new economic governance plan (now officially called Euro Plus Pact), the EU drew up different coordination schemes to prevent the emergence of sizeable financial imbalances[1]. Essentially, the EU has to decide whether it will be a true Union, or whether the "weak links" in this Union will have to be left behind.

European identity*:* A potential obstacle to a joint response to the financial crisis and how this affects the performance of clinical research, is the fact that the EU represents a diverse group of people with different social, cultural and political backgrounds, which do not necessarily have the "common cause" motivation seen among different groups in the US.

Inadequate financial tools*:* At the Lisbon European Council in 2000 the EU announced the ambitious goal of becoming by 2010 the most dynamic and competitive knowledge-based economy in the world. One of the projects launched at the Lisbon Council was the European Research Area (ERA), as a means to establish a reference framework for research in Europe, recognizing that the EU was behind the U.S. and Japan in research and innovation performance. Expenditure in Research and Development (R&D) was 1.9% of Gross Domestic Product

(GDP) by then, compared with 2.7% in the U.S. and 3.1% in Japan[2]. This has not been successful as the EU armed only with the Framework Programme (FP) and the ERA, together with national research policies very loosely coordinated with EU policies, has not been able to meet these goals. To a large extent responsibility lies with a stubborn reliance on national funding for universities and clinical research and an inability to get the private sector more involved in conducting and financing research.

Bureaucracy: In a report to the government, January 2011, the Academy of Medical Sciences in the UK, said that bureaucracy and complexity are "stifling" health research in Britain and driving clinical trials abroad, without any benefits for patient safety, especially given the current financial crisis[3]. The academy recommends replacing the plethora of approval processes with a health research agency that would cover the ethics and governance of medical research. One problem was the European clinical trials directive, which took effect in 2004 and was implemented more restrictively in the UK than elsewhere[4]. The European Commission is reviewing the directive. Additionally, each individual NHS trust taking part in a research project insisted on carrying out its own elaborate checks, delaying the approvals process. The net result, according to the report, was that Britain's share of patients taking part in clinical trials globally fell from 6 per cent to 2 per cent over the past decade. The Cancer Research UK group estimates that unnecessary regulation adds 10 per cent to the costs of conducting medical research in Britain[5]. On average it takes the charity two years to start a clinical trial, after making a research grant. This delay in the bureaucracy has led to a decrease in the number of clinical trials in the EU from 5,028 in 2007 to 4,193 in 2010, a decrease of 17% [6].

"Outsourcing" clinical research: Rising financial and regulatory pressures on western pharmaceutical industry appears to drive the clinical trial market towards Asia. In Europe, 61% of patients taking part in clinical trials that were submitted to the European Medicines Agency were from countries outside the European Union, including Eastern Europe and Asia[7]. China, over the last decade, has developed significant capabilities in clinical trials, along with some improvements in project and data management. China can provide cost savings of 50-60% for clinical trials, and with discovery research occupying around one third of the R&D expenditure of western pharmaceutical companies, outsourcing to low cost countries is logical[8]. However, this has raised some concerns as the local research environment and standards need to be carefully examined in a lot of these countries, and the results can also be affected as patients in different countries may be taking additional medications that can affect the results. This means that it may not always be possible to draw conclusions about medications or trial results regarding the European population based on data obtained in different countries.

The case of Greece or "where they say it all began": Greece appears to be at the center of the storm and for many the culprit. However, once clear thinking prevails it becomes apparent that Greece was only the first (and perhaps easiest) victim in this new type of financial warfare. No matter what the correct explanation of the role of Greece, the fact remains that the picture of health care in Greece is deteriorating, especially for the most vulnerable groups in society[9]. Specifically, there is reduced access to health care, which appears to be the result of significant and, arguably, necessary cuts (almost 40%) of hospital budgets[10,11]. These reduced budgets are further overburdened by a shift of patients from private to public health care providers[12]. This is also evidenced by an increased use of street clinics (30% up from 4% before the crisis), which were previously used mainly by immigrants[13]. In such an environment of increasing need for public health care, which cannot be easily met, the role of health care research becomes even more important, yet its future remains uncertain.

Impact on European Academia*:* The European Universities Association (EUA) has been monitoring the effects on higher education in Europe arising from the evolving economic crisis since 2008, and in a recent report highlights the impact from country to country[14]. Whilst this may reflect to some extent the impact of the crisis on different national economies, universities have been affected at different stages of the crisis. Some universities were impacted as early as the beginning of 2009 while others were impacted later. Overall, institutions in most countries report being faced with uncertainty and expect further cuts, and some countries demonstrate that cuts are likely to have a deep re-structuring effect on higher education systems. In Italy, universities' public funding is expected to be reduced by close to 20% by 2013, while at the same time diminishing universities' income from tuition fees, which are limited and cannot exceed 20% of public funding[15]. This could lead to the default of some 25 universities in the near future. The EUA monitoring has been able to identify 5 main categories which show the effect of the economic crisis on public funding of universities across Europe. These include university mission, teaching, research, autonomy and private funding. On average teaching seems to have been more affected than research. This change is of particular concern at a time when economic downturn has increased demand for higher education. The report, Financially Sustainable Universities II: European Universities Diversifying Income Sources, is the outcome of a two-year EUA study of how higher education is currently financed and what its expectations are[16]. More than 150 institutions in the 27 European countries were surveyed. It also analyses the many different barriers that prevent universities from seeking additional income sources. There are concerns for the public funding of research. Some 41% of universities believe it will remain stable, while nearly a third (30%) expect state funding for research to fall.

Nearly half of the universities surveyed expect additional sources of funding (non-public funding) to grow.

Strategies which are beginning to emerge in some countries involve Universities managing reduced funding by closing some departments or merging institutions. There have been impacts on research. In some countries expenditure has been reduced. Some countries have increased programs aimed at promoting innovation. Funding authorities seem to be increasingly using competitive funding programs as the basis for allocating research funds. Overall the changes described in detail in the report reveal not only that public economic support of universities is diminishing but also changing in the nature and form in which it is available[16]. Increasingly there are conditions attached to it and growing accountability requirements. As a result funding is targeted to achieve specific objectives, usually along the lines of national strategic priorities. This has given national governments increasing guiding influence over the universities, with potential threats to academic autonomy. The latter goes hand in hand with financial autonomy and can be the prerequisite to overcome the crisis by allowing universities the ability to allocate their funds along the lines of their institutional missions. In addition to the decrease in public funding there appears to be a decrease in donations from philanthropic and other foundations, as their financial support base has in turn been affected by the crisis[15]. Specifically, in the United Kingdom private income for universities from alumni donations and fundraising activities has fallen by one fifth according to some estimates[17].

Potential solutions: From a brief analysis of the effect of the financial crisis on conducting clinical research and development, it is obvious that it is not simply a matter of adequate funding. There are significant changes needed in the framework that research is conducted within, as well as adaptive measures by all parties involved, including the European Union, universities and private industry. There is some light at the end of the tunnel, as the following potential solutions may show.

"Europe 2020" project*:* The aim of the "Europe 2020" project is to identify ways to remove barriers from clinical research and technology transfer and sustain innovation, with small and medium-sized enterprises (SMEs) and universities as the engine of innovation[18]. The financial crisis coupled with escalating costs of clinical trials and the long time-frame for the development of health care products constitute a challenging environment. Solutions within the Europe 2020 agenda include a single market for innovation and the completion of the ERA. Funding would also be better coordinated along the innovation chain - from basic research down to launching new products and services on the market. Simplified procedures and rules would make it easier for researchers, companies and entrepreneurs to cooperate, apply for and use EU funding. Performance checks would monitor projects to ensure taxpayers' money is being used effectively. The Commission's approach also involves creating public-private partnerships to bring more innovations to market faster. The first partnership, to be launched in 2011, will encourage R&D to develop new products and services for active and healthy ageing. The EU will encourage governments and industry to increase overall investment in R&D to 3% of the GDP by 2020 (from 2% in 2009). Achieving that target could create 3.7 million jobs and boost annual growth by up to €795 billion.

Major instruments include the FP for research and the Competitiveness and Innovation Programme (CIP). Specifically, FP 6 sees over 6 billion € allocated to cooperative health research for the period 2007 to 2013. Additionally, FP 7 has seen the establishment of the Innovative Medicines Initiative (IMI) Joint undertaking, which is a combined effort by the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA)[19]. This is an innovative attempt to solve complex problems associated with the need to modernize and improve the drug development process. Furthermore, the EU is currently undertaking a review of the 2001 Clinical Trials Directive and this is an excellent opportunity for change[20]. For the first time some € 100 million of EU funding will be made available this year for multi-national trials and will cover a 4 year period. At the same time it is an opportunity to foster better multinational cooperation in clinical research.

The EU realizes that in order to become more efficient within the limits of today's financial constraints, the only option is to invest in innovations of the system. Along these lines, there was the "Innovation in Healthcare: from research to Market" conference in March, 2011, which together with the input gathered through the open consultation on the Green paper entitled "From Challenges to Opportunities: towards a common strategic framework for EU research and Innovation funding" aim to design the proposals for the next generation of EU funding schemes that will be presented by the Commission to the Council and Parliament before the end of 2011[21, 22]. This Green paper has the goal of focusing on research and innovation and address how these can be advanced, while ensuring that funding programs focus on Europe 2020 priorities, address societal challenges and important technologies, facilitate collaborative and industry-driven research, simplify the instruments and bureaucracy involved, and reduce the time to the market[22]. It is essential to underscore the fact that, no matter what the financial situation, research should remain curiosity-driven, rather than driven by the available funding options.

Role of the European Commission Science Advisory Board in Health*:* The European Commission's independent advisory board on health research witnessing the increasing health challenges that Europe is facing, the fact that US investment in biomedical research as a proportion of gross domestic product is almost three times higher than that in Europe, and that competition

from China, Brazil, Russia, Singapore and South Korea is intensifying, has presented recommendations to improve Europe's profile in biomedical research in these times of financial hardship[23]. These include the following proposals:

- The share of the European Framework Programme for biomedical research should reflect the biomedical fraction of the ERA (35%).
- Increase and improve the teaching of biomedicine.
- Develop career structures and increase mobility to recover young talent from the USA and elsewhere.
- Create research partnerships for MDs and PhDs.
- Minimize the administrative burden for clinical trials, in particular multinational and investigator-driven clinical trials.
- Create funding and reward systems for small and medium sized enterprises to strengthen research-based innovation.
- Increase biomedical research investment as a way to overcome the financial crisis through promoting and sustaining development.

A new model of cooperation among the parties involved: Financial difficulties, compounded by an ageing population, will lead to changing the old European concept of universal access to health care for patients to one of finite health care budgets. There is a critical need for international clinical trial collaborations to reach critical mass to accelerate the development of targeted drugs. The European Union, given the number of countries involved, is in a unique situation to implement that. However, in order to be successful the incredible bureaucracy needed to launch international trials must be decreased. With this goal in mind, international cooperation is an important aspect of FP7 as there is encouragement to include organizations from the International Cooperation Partner Countries and from countries with scientific and technological cooperation agreements with the EU[24]. Equally critical is the need to form partnerships between academia, patients' organizations, representatives of regulatory agencies and governments, so as not to leave the whole burden to the pharmaceutical industry. Universities can and should play a very important role in this restructuring as it can be seen in the next paragraph.

The role of Academia: In the model of international cooperation mentioned above, members of the international scientific community need to realize the danger posed to health care research by this international crisis for every single country. More importantly, they need to realize that this is an issue without national boundaries and as such, the international research community should have a strong voice. Along these lines there have been efforts, such as the one by the Greek National Council for Research and Technology, to obtain support from the international scientific community in stressing the fact that pressure applied harshly can lead to indiscriminate financial cuts. This would lead to a dramatic decrease in any research or scientific endeavors that essentially are our lifeline for any meaningful future recovery[25].

University research funding*:* Serious concern has been expressed about public funding for teaching. As the financial crisis deepens the European model of academic research, whereby the main source of funding is public, will not be able to sustain meaningful clinical research. In order for this to continue there is agreement that there will need to be greater cooperation between academia and governmental authorities on one hand, and pharmaceutical companies and small and medium sized enterprises on the other hand. This model that is similar to the U.S. one, will require suitable internal and external structures to raise and manage funds in an appropriate way. This will increase clinical research productivity exponentially, overcome the limitations of the financial crisis –while at the same time stimulating the economy- in a way that spreads the financial risk between different partners, thus engaging them all in the success of the system.

To achieve that it is imperative that there is a change in the culture of conducting clinical research in Europe. A lesson can be learnt by comparing the American and European research systems. The diversity of the U.S. public research system, a very mobile scientific labor force, and a large number of policy initiatives promote commercialization of academically-originated research, mainly through the involvement of small and medium size enterprises. The guiding principle through all of this remains the need to maintain a close link between goal-oriented therapeutic research with fundamental biological investigation. Financing, even for public universities, in the U.S. originates from a wide range of resources, including state and national governments, foundations, corporate supporters, tuition revenues, alumni gifts, and generous endowments. Faculty members in the U.S. have much more research independence at early career stages, as well as increased mobility in order to better their market position. In contrast to this model, in Europe younger scientists have much less mobility, which also means significantly less research independence. In Europe industry-university relations have lagged behind, mainly due to legal prohibitions in the past against collaboration with commercial entities, as well as cultural predispositions about the value of knowledge for its own sake. Additionally, national clusters of specialists may have benefited in Europe from the accumulated advantage of talent and funding; however, the funding sources were largely national rather than European, which means that the research goals and priorities were also a matter of national policy, rather than a common European one. Although not perfect, it certainly appears that there are a lot of lessons that a unified European approach towards research can learn from the U.S. model.

Conclusion

We currently find ourselves in a time of crisis for the national and global economy, which has and will con-

tinue to affect clinical and basic science research. However, we cannot allow this to happen as we need to realize that research goes hand in hand with development. The latter is sorely needed as it is an integral part of the effort to overcome this economic downturn. For these reasons, this difficult time should be seen as an opportunity to change and improve the way that we conduct research. Specifically, it is essential to have a common European policy for research (and not simply in addition to national guidelines), limit bureaucracy, make use of increased funding from the ERA, focus attention on the career structures of young scientists and avoid a brain drain and, last but not least, create a viable, cooperative and synergistic relationship between academia, industry and small and medium size enterprises.

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