

INDEPENDENT CLINICAL RESEARCH: A ROAD TOWARDS AFFORDABLE & VALUABLE MEDICINES

INTRODUCTION

The current system of industry-based clinical research for new medicines is expensive and ineffective. It results in expensive medicines with little to no added therapeutic value. Moreover, some of the biggest public health challenges remain unaddressed.

Many of the deficiencies in the current system can be attributed to the fact that new medicines have been developed and marketed by private companies, whose main concern is their shareholder value. Wemos advocates independent clinical research of new medicines. In this paper, we will argue why.

THE SYMPTOMS

The market continues to be flooded with expensive new medicinesⁱ. In spite of measures to contain health care expenditure on medicines, most governments see the costs for medicines taking up ever greater parts of the health care budgetⁱⁱ. Ironically, the most expensive categories of medicines, like new cancer treatments, are becoming proportionally more expensive than cheaper ones.

At the same time, 'over two thirds of new medicines reaching the market do not represent any therapeutic advance for patients, with many patents based on a reshuffling of old combinations for additional uses for existing ones'ⁱⁱⁱ. So we're paying more money for less value.

To make things worse, many public health challenges, such as neglected diseases and growing antimicrobial resistance^{iv}, are not being addressed by the new drugs on the market.

THE CAUSES

The root causes of these symptoms lie in the flawed system in which medicines are developed, produced, authorized and marketed. The medicines system is treated as a free market, where - ideally - the demand will dictate what will be supplied and where prices will drop when there is enough competition. Unfortunately, this is not currently the case.

The medicines market is a market where the manufacturers have been granted many benefits, such as secrecy of research data and lack of transparency about costs for research and development (R&D). This information is often considered part of the industry's

intellectual property or trade secret, and therefore protected. And without transparency about R&D costs, manufacturers might set their prices according to what societies are prepared to pay for them, knowing that every health care system needs medicines and that a continuous flow of new cures is expected by both doctors and patients. Especially the rise in chronic diseases presents a huge market opportunity.

Consequently, pharmaceutical industries are keen on introducing new medicines. In accordance with European Union (EU) legislation, medicines are evaluated based on their quality, safety and efficacy before they are granted marketing authorization by the European Medicines Agency (EMA)^v. Added therapeutic value (ATV), i.e. the advantage of the new drug compared to existing treatments, is not assessed. In The Netherlands, the National Health Care Institute is the national body that determines and advises on which types of health care are or are not included in the basic care insurance package (their motto: *taking care of good healthcare – no more and no less than necessary*)^{vi}. They do consider added therapeutic value, but more often than not, they lack solid research data to assess this and resort to the ‘non-inferiority’ criterion^{vii}: meaning that a new drug that is equally effective as existing treatments can qualify for inclusion in basic care.

This is caused by the fact that market authorization may be granted on the basis of research done by the manufacturer itself. This presents potential conflicts of interest. Studies show that for-profit-funded clinical trials yield more positive results than non-profit and mixed source-funded trials, and that side effects are not as properly registered. This difference is associated mainly with the use of surrogate endpoints in for-profit- financed drug trials.^{viii} An example of this is the claim of weight loss for an antidiabetic drug, with no proven effect on a hard clinical endpoint like macrovascular disease (myocardial infarction). Another obstacle to assessing ATV is the publication bias towards positive results. Negative or questionable results are less frequently published in peer-reviewed journals, while these data are obviously indispensable for determining their ATV.

Last but not least, pharmaceutical companies are allowed to remain secretive about the true costs for research and development of new medicines, a principal factor in determining their cost price. This makes it difficult to evaluate whether medicine list prices can be considered reasonable. The current patent system pushes prices further up.

THE CONSEQUENCES

Pharmaceutical companies go for blockbusters: medicines with high profit potential. High profit is possible when new medicines are actually only slightly different from previous products, with low R&D costs, preferably in combination with a large group of potential buyers. The increased prevalence of chronic diseases presents a very attractive market opportunity, because drugs that treat risk factors or chronic illnesses, such as high blood pressure, high cholesterol and diabetes, are taken daily for the rest of a patient’s life.

A common tendency is also to stretch the boundaries of illnesses and raise public awareness of those ailments in order to enlarge the market for treatment, and even to create new ‘diseases’, commonly referred to as disease mongering. Medicines for conditions that do not

seriously influence quality of life, and are not generally considered a public health priority, are brought to the market at low costs for the manufacturer, at considerable prices, resulting in high profits.

As these easy markets are within reach, pharmaceutical companies are less inclined to invest in the development of treatments for niche markets: diseases that have long been neglected, require real breakthrough treatment, and affect only a limited number of people, especially in low-income countries. Another example of a public health priority is the need for new antibiotics. As the rate of antimicrobial resistance is rising globally, the development and production of new antibiotics are extremely important. However, antibiotics have a poor return on investment because they are taken for a short period of time and cure their target disease^{ix}, which makes their development less attractive for pharmaceutical industries.

Not only are new and much needed new treatments not researched, other public health research priorities are scarcely addressed in for-profit based clinical research. Examples are: clinical trials on cost-effectiveness issues; head-to-head comparisons of different medicines; clinical trials enhancing the use of a certain drug; clinical research on medicines for rare or tropical diseases, elderly patients, children and pregnant women; and clinical research on off-patent medicines.

Last but not least, the protection of research data associated with obtaining market exclusivity frustrates the advancement of clinical research, leads to inefficient use of research data and increases the marginal costs of clinical research.^x On this behalf something changed in the EU due to legislation in October 2016. The European Medicines Agency (EMA) now publishes clinical data submitted by pharmaceutical companies to support their regulatory applications for human medicines under the centralised procedure.

THE CURE

Wemos advocates independent research as an important step forward towards curing a flawed system. We acknowledge that a system based entirely on publicly funded research is unrealistic, at least in the near future, but tackling the inefficiencies in the current system in an income-neutral way should be a good starting point.

We are currently studying whether it is feasible that market authorization application files include the results of at least one independent clinical trial. Independent research consistently yields clearer results and less false positive outcomes, for the simple reason that the funder has no personal interest in the outcome. Regulatory authorities should therefore demand from the industry that one clinical trial is conducted by an independent research institute in each pivotal phase three trial. This allows health technology assessment institutions to determine the actual value of a new drug. A comparison with existing treatments will increase the quality of research by assessing explicitly the added therapeutic value of a medicine.

The funds for such research can be raised in various manners, as we have seen in several European countries. In Italy, the Italian Medicines Agency (AIFA) obliges all Italian-based pharmaceutical companies to pay five percent of their marketing expenditures as a tax, to fill a fund for independent research. In the United Kingdom, general taxation is used for the execution of publicly funded clinical research under the auspices of the Ministry of Health. Because of the UK's National Health Service system, the government directly benefits from publicly funded clinical research, leading to cost-reductions in the health sector. In Belgium, Minister of Health Maggie De Block commissioned the Federal Knowledge Center for Health Care (KCE) to carry out a program of practice-oriented clinical studies^{xi}. For this purpose, she released a budget of € 5 million for the period 2016-2017.

SIDE EFFECTS

Public funding of clinical research allows for better prioritization of actual public health priorities. It will also put more emphasis on true ATV and cost-effectiveness, and not incentivize clinical trials for marketing purposes or for drugs with limited ATV. A data sharing requirement will lead to greater transparency and advance scientific knowledge. Obscuring or concealing of unwelcome research results will become more difficult. Public funding of clinical trials saves money by providing transparency on actual R&D costs and by lowering the requirements on return of investments. In combination with limitations and changes in the patent system, a huge reduction of drug prices could be achieved, with obvious benefits to the health sector as a whole.

PRECAUTIONS FOR USE

Wemos believes that there is a momentum in society, including at political levels, for tackling the flawed R&D system for medicines. Big changes are needed, which present numerous challenges. It will require an independent research co-ordination agency and quality control mechanisms, for which investments and expertise are needed.

Also, changes in the market authorization procedures may be necessary. At present, the assessment of the efficacy of a drug requires two studies with positive outcomes, while there may also be research data with neutral or even negative outcomes. Negative and positive outcomes are not weighed in order to reach an overall conclusion on efficacy and ATV.

Another challenge for conducting independent clinical trials is the process design for priority setting. In some European countries, mechanisms are already in place for this. In the United Kingdom, the Health Research Program of the National Institute for Health Research calls for proposals and funding proposals for researchers. The panels responsible for prioritization consist of NHS managers, patients, doctors and nurses, but not academics. In Italy, priorities are set via hearings with scientific stakeholders, as well as via website consultations. In the example of Italy, intellectual property rights of innovative products originating from the calls are owned by the researchers who conducted the clinical investigation.

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ⁱ BMJ2015;350:h2068

ⁱⁱ <https://www.nza.nl/publicaties/nieuws/Kosten-dure-medicijnen-blijven-stijgen/>

ⁱⁱⁱ Mazzucato Mariana. High cost of new drugs BMJ 2016; 354 :i4136

^{iv} http://www.who.int/medicines/areas/rational_use/antibacterial_agents_clinical_development/en/

^v http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/document_listing/document_listing_000426.jsp&mid=WC0b01ac058001ce7d

^{vi} <https://english.zorginstituutnederland.nl/>

^{vii} Personal communication [Zorginstituut Nederland aan Ella Weggen]

^{viii} Delgado, A. F. & Delgado, A. F. The association of funding source on effect size in randomized controlled trials : 2013 – 2015 – a cross-sectional survey and meta- analysis. 1–9 (2017). doi:10.1186/s13063-017-1872-0

^{ix} WHO. Race against time to develop new antibiotics. Bulletin of the World Health Organization 2011;89:88–89. doi:10.2471/BLT.11.030211

^x Kei. PROPOSAL 6 Clinical Trials on Medicines as Global Public Goods Table of Contents. 4, 2007–2008 (2008)

^{xi} KCE research proposal 2015: <https://kce.fgov.be/publication/report/publicly-funded-practice-oriented-clinical-trials>