

He who pays the piper calls the tune?

On funding and the development of medical knowledge



Monitoring Report Ethics and Health 2009

CENTRE FOR ETHICS AND HEALTH

He who pays the piper calls the tune?
Edition of the Centre for Ethics and Health
ISBN 978-90-78823-12-4

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Preferred citation:
Health Council of the Netherlands. *He who pays the piper calls the tune?*
Monitoring Report Ethics and Health, 2009/3. The Hague: Centre for Ethics and Health, 2009

Publicatienummer Health Council of the Netherlands: 2009/18

This publication can be downloaded from www.ceg.nl / www.healthcouncil.nl / www.rvz.net



Centre for Ethics and Health

To the Minister of
Health, Welfare and Sport

Minister,

This advisory report is an initiative of the Health Council of the Netherlands' Standing Committee on Medical Ethics and Health Law. The advisory report examines the influence of sponsoring, industrial or otherwise, on the development of medical knowledge, and the ethical questions to which this gives rise. It is mainly concerned with the stage of setting the agenda and priorities for the knowledge that should be developed and the stage of developing that knowledge through research.

Case studies are used as the basis for demonstrating that the development of biomedical knowledge would be unbalanced, if knowledge development became excessively dependent on industrial research. The case studies concern drug research, research into diagnostic devices, nutritional research and public health research. The fields of knowledge studied appear to be subject to all the consequences of the *crowding-out effect*: the phenomenon that in fields of knowledge in which product sales and making profit play little, if any, role, development lags behind development in economically valorisable fields of knowledge, even if society has a definite need for the knowledge concerned.

These findings give rise to ethical questions, such as about the extent to which the described effect leads to an imbalance in choices and results concerning knowledge development and to possible restrictions on setting research priorities. Questions of this kind need to be discussed in greater detail.

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Presentation Horizon
scanning report

With regard to the influence of industrial sponsoring on research, reference literature shows that when a company funds research into one of its own products, the results are more favourable for the product concerned than the results of alternatively funded research concerning the same product. This distortion in favour of the sponsor's product is disturbing, also because it can undermine trust in research. The important ethical question therefore arises of what the implications of this are for the conduct of the various parties concerned: researchers and their institutions, journals and their editorial staff, industry and government.

The advisory report provides suggestions on how the identified problems could be tackled. The question always revolves around the contribution that the parties concerned can make to possible solutions. Government can steer some aspects of this.

This advisory report is part of the CEG's series of Ethics and Health Monitoring Reports. It was compiled under the responsibility of the Standing Committee on Medical Ethics and Health Law. It was reviewed by the Advisory Council on Health Research and the Standing Committee on Medicine. The case study on nutritional research was discussed with the Standing Committee on Nutrition, while that on public health research was discussed with the Standing Committee on Public Health.

Yours faithfully,
(signed)
Prof. J.A. Knottnerus

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Executive summary

This advisory report examines the influence of financiers (especially industrial financiers) on the development of medical knowledge, and the ethical questions to which this gives rise. This also especially involves deciding on which fields of knowledge need to be developed and the actual development of that knowledge through research. The words 'sponsoring' and 'sponsor' are used below to refer to research 'funding' and the 'financier'. This advisory report is based on a background study commissioned by the Health Council of the Netherlands which was conducted by Professor R. Bal *et al.*, as well as a study of reference literature and interviews with experts. The Health Council of the Netherlands' Standing Committee on Medical Ethics and Health Law compiled this advisory report. It has been published under the aegis of the Centre for Ethics and Health (CEG), a partnership between the Health Council of the Netherlands and the Council for Public Health and Health Care. The Health Council of the Netherlands is responsible for the content.

Agenda influences

Chapter 1 emphasises that besides industrial sponsors, other parties, such as government and charitable funds, also finance research and therefore influence the research agenda. Particular interests and compromises may also play a role in government decision-making concerned with setting the agenda and priorities for research paid for with public funds (which public interest should be given priority?). The fact that charitable funds exist for some diseases and not for others may also lead to distortions in knowledge development. Issues of this kind are also worthy of attention but are only discussed briefly in this advisory report.

Industrial sponsoring

Chapter 2 explores the influence of industrial sponsoring on the composition of the research agenda. It is precisely in this initial stage of knowledge development that the prescriptive character clearly comes into focus. Industry especially tends to take an interest in subjects and develop fields of knowledge which can be expected to earn money within the foreseeable future. This is understandable, given that a business has to be profitable to ensure its continuity. The public health knowledge requirement mainly plays a role in the composition of the industrial research agenda where need coincides with commercial feasibility. Commercial feasibility and social importance are compatible but the development of biomedical knowledge

would be unbalanced if knowledge development became excessively dependent on industrial research. This would also have adverse consequences for the quality of prevention and care.

The warning against lopsided knowledge development is substantiated by four case studies: drug research; research into diagnostic devices; nutritional research; public health research. Gaps in knowledge developed in these fields are delineated. Possible downsides of increased interrelatedness between industrial and clinical research are also pointed out. There is a risk that the size of the fees paid by industry may carry some weight in the composition of the clinical research agenda and could thereby detract from the attention paid to the social benefit and quality. Possibilities and limitations of Public-Private Partnerships (PPPs) in which research projects are carried out jointly by the public and private sector are discussed. The PPP model is especially suitable for research that is likely to produce economically valorisable results in due course. The model is not a remedy for research for which the results are definitely not commercially marketable, such as research into collective public health interventions.

Unbalanced growth in biomedical knowledge

Chapter 3 summarises the main results of the four case studies. The fields of knowledge studied are subject to all the consequences of the crowding-out effect: in fields of knowledge in which product sales and making profit play little, if any, role, development lags behind that in economically valorisable fields of knowledge, even if society has a definite need for the knowledge concerned. The following factors play a role in this:

- 1 Industry tends not to conduct more research than is required for a new product's registration, as in the case of drugs and diagnostic devices;
- 2 Possibilities for patenting are limited in certain fields, as in the case of research into the effect of foods on health;
- 3 Demand for commercial products is sometimes too low in certain domains, such as public health.

These findings give rise to ethical questions, such as about the extent to which the crowding-out effect leads to imbalances or even unjustifiable choices and results concerning knowledge development, possible restrictions on free choice of research priorities, and the responsibility of government and other parties to make adjustments. This and similar questions would need to be discussed in greater detail.

In the process of knowledge development, the stage of conducting the research follows that of setting the agenda and priorities. International literature has shown that when a company funds research into one of its own products, the results are more favourable for the product concerned than the results of alternatively funded research concerning the same product. This distortion in favour of the sponsor's product is disturbing, also because it can harm trust in research. Explanations of why sponsored research significantly more often produces better

results for the sponsor's product are found at three levels: comparisons using a placebo instead of an active drug; selective publication of research results that are favourable for the sponsor; and the selection of a favourable comparison, as when an inadequate dose of the other drug used in the comparison is administered.

The fact that reference literature revealed results favouring sponsors' products also raises ethical questions. What implications do these results have for the conduct of the various actors, such as doctors/researchers and their institutions, science journals and their editorial staff, sponsors/manufacturers and government? The parties concerned will have to engage in debate about this.

Suggested solutions

To conclude, chapter four includes suggestions on how the identified problems could be tackled. The question always revolves around the contribution that the aforementioned actors can make to possible solutions. Government can direct some aspects but changes in the attitude of professionals and the role of industry are also important.

The potential research capacity and the number of available trial subjects/patients in biomedical research are limited. In view of the results of the case studies and the crowding-out effect, the concern is that the available capacity is not always used to generate the most urgently needed knowledge from the public health point of view. Consequently, the aforementioned actors should jointly reflect on their role and responsibility in funding biomedical research and setting the agenda and priorities. Various options for the parties concerned to combat the crowding-out effect are discussed. The parties must be persuaded that seeding trials (which are sponsored trials with the sole object of getting doctors to prescribe a registered product) produce no new knowledge and cannot therefore be scientifically justified.

Distortions in research results in the case of industrial sponsoring can be combated by preventing any research project intended to find research results that are favourable for the sponsor. The parties concerned can also help with this in their own way. The necessary steps towards achieving this have been made in recent years. If an accepted alternative treatment is available, placebo-controlled trials should be further reduced; research results that are disappointing for the sponsor should also be published; the optimum dose must be administered of the drug with which the comparison is being made.

The main assurance against distortion of this kind is the researcher's independence. Reducing conflicts of interest between the sponsor and the researcher reduces the need for the researcher to be 'agreeable' to the sponsor, which reduces the likelihood of bias in research results. Conflicts of interest may arise through personal reward, for example, or other forms of financial support, such as opportunities to attend congresses and payment of the associated costs. Doctors/researchers should adopt a more assertive and aloof and thereby more inde-

pendent attitude towards sponsors. Another important development is that ongoing studies are increasingly being made public through trial registers, which have to report conflicts of interest and sponsoring.

1 Introduction

1.1 Background

Scientific knowledge and knowledge development are essential for promoting public health and health care and for government policy with that objective. The Health Council of the Netherlands has the task of advising government and Parliament on the latest scientific developments concerning public health. Since the Health Council of the Netherlands merged with the Advisory Council on Health Research (RGO) in 2008, its tasks have also included advising on health research priorities. The Health Council of the Netherlands therefore not only assesses the substance, reliability and quality of available knowledge but also advises on the public health 'research agenda', which indicates where there is a need for new knowledge and how it can be met.

Knowledge development is not a neutral, separate phenomenon. Prescriptive processes also influence the establishment of the research agenda. Particular interests play a role too, in addition to social values and norms, such as the aim of providing proper health care. Commercial influences also have an impact. After all, given the major significance of scientific knowledge for care-related markets – as in the fields of drugs, diagnostic devices and foods with health claims – commercial companies have a considerable interest in generating medical and health care knowledge. Commercial companies have therefore long been involved in Research & Development (R&D) and sponsoring scientific research. This is not guided solely by public health requirements but equally by the anticipated prospect of profitably marketing the knowledge obtained and the resulting products.

This process has produced a great deal of knowledge and many opportunities of importance for public health but there are also risks. This is because scientific knowledge production that is directed too much by commercial interests – possibly in the form of PPPs – can be an obstacle to ensuring the independence, reliability and balance of knowledge development and the public health research agenda. Sooner or later this can have consequences for public health.

Various prescriptive angles of approach are possible for studying how the knowledge agenda and knowledge production are affected by research sponsoring:

- The approach to the subject studied. The incentive to study a particular subject will be greater when the valorisation and potential profits expected to be obtained from the results are higher. Research depends heavily on public funding when it concerns subjects involving little, if any, anticipated profit, such as long-term *public health* interventions relating to behaviour changes. Public funds are relatively modest, as is their duration. The question arises as to whether existing social flows of funding for research are commensurate with the social importance of the research concerned and whether there might be an imbalance. Consider for example the mechanism whereby the public implicitly funds the continuity of R&D in the pharmaceutical industry through drug prices, while no such mechanism exists for funding R&D into interventions in the field of public health and care.
- The approach to the available research capacity. There are limits to the extent to which clinical researchers but also doctors and patients can participate in research. An increase in the extent to which this capacity is used for commercially oriented research – for which attractive research budgets and payments per included patient are generally provided – decreases the field of play for other research. Consequently, the choices which research institutions and individual researchers make in connection with this have prescriptive implications.
- The approach to the research results. Many scientific publications have appeared in recent years that indicate a relationship between the type of sponsor (commercial or otherwise) and the results of the research conducted.
- The approach to reporting and disseminating research results. The results of sponsored research are not always published and disseminated through accessible scientific channels as a matter of course.

This advisory report on ethical concerns has been written against this background. The prescriptive angle of approach involves bringing forward observations and points for agendas in relation to how sponsoring, industrial or otherwise, influences medical and health research. Observations raise fundamental ethical questions about the degree to which the parties concerned are allowed to set their own research priorities and about the responsibility to adjust these (sections 3.2 and 3.5). The focus is particularly on the implications for the public health research agenda. Key fields which jointly account for a considerable portion of health research are used as an example, namely

- drug research
- research into diagnostic devices
- research relating to healthy food
- public health research in general.

Besides industrial sponsors, other sponsors such as government and charitable funds also influence the agenda for research and its execution. The fact that, for example, charitable funds, such as collection-box funds, exist for some diseases and not for others may also lead to distortions in knowledge development. All kinds of particular interests and compromises may also play a role in government decision-making concerned with setting the agenda and

priorities for research paid for with public funds (which public interest should be given priority?). Issues of this kind are also worthy of attention but are only discussed briefly in this advisory report, namely in connection with seeking balance between public and private funding.

1.2 Question and aim

The question is: what is known about the implications of the system of industrial sponsoring for the development of biomedical knowledge, and what ethical questions does it pose? A distinction is made between four stages in knowledge development, namely

- a Setting the agenda and priorities for the knowledge that should be developed;
- b Developing that knowledge through research;
- c Disseminating the knowledge (which includes disseminating research results and education); and
- d The knowledge's practical application, including through the development of directives.

This distinction is clarifying but rather artificial. The process is actually cyclical and the various stages overlap. This advisory report focuses primarily on the first two stages (a. setting the agenda and priorities, and b. knowledge development through research) and on the third stage (c) insofar as it concerns the publication of research. These are the issues that are closest to the core business of the Health Council of the Netherlands. A recent RVZ report placed the emphasis more on the third and fourth stages.¹

The terms 'sponsoring' and 'sponsor' have the meaning of 'funding' and 'financier' in this advisory report. This meaning differs from that given in the Good Clinical Practice (GCP) Directive. The GCP Directive defines 'sponsor' as: *An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.*

This advisory report is intended to draw attention to the issues concerned and to explore them.

1.3 Approach

This advisory report is based on a background study commissioned by the Health Council of the Netherlands and conducted by Professor R. Bal *et al.*, as well as a study of reference literature and interviews with experts. The background study can be consulted on the websites of the Centre for Ethics and Health (<http://www.ceg.nl>) and the Health Council of the Netherlands (<http://www.gezondheidsraad.nl>). The names and positions of the interviewees are provided in annex 1.

1.4 Accountability

This advisory report was drawn up by the Health Council of the Netherlands' Standing Committee on Medical Ethics and Health Law. It was revised by the Advisory Council on Health Research and the Standing Committee on Medicine. The case study on nutritional research (2.7) was discussed with the Standing Committee on Nutrition and the case study on public health research (2.8) was discussed with the Standing Committee on Public Health. The advisory report has been published under the aegis of the Centre for Ethics and Health (CEG), a partnership between the Health Council of the Netherlands and the Council for Public Health and Health Care (RVZ). The Health Council of the Netherlands is responsible for the advisory report's content.

2 Industrial sponsoring and the research agenda

Following the sections on agenda-setting (2.1) funding (2.2), clinical research (2.3) and the role of public-private partnerships (2.4), in this chapter we explore how the method of sponsoring influences the research agenda in various fields of medical knowledge. It involves four case studies, namely Drug research (2.5); Research into diagnostic devices (2.6); Nutritional research (2.7); and Public health research (2.8). This leads to the identification of knowledge gaps.

2.1 Setting the agenda and priorities

The first stage of knowledge development is that of setting the agenda and priorities. This stage is crucial for the entire process. This is because there is little chance of research being conducted into a subject or field that has not been identified as potentially interesting or significant, and without research no knowledge of that subject or field will be developed. Despite the importance of this stage, it has been studied much less than the other stages.

As already established, knowledge development is not a neutral phenomenon. The process through which knowledge becomes available to promote health and good care is directed, consciously or otherwise. These possibly implicit steering mechanisms have prescriptive implications. The question of how the flow of knowledge is influenced is a socially prescriptive issue. The first stage of knowledge development, that of setting the agenda and priorities, is precisely where the prescriptive feature of the process is seen most clearly. We explore this feature here while primarily looking for knowledge gaps.

The development of medical possibilities, especially drugs, largely takes place through corporate production. This has led to some remarkable successes which are of benefit to many patients every day. However, at the same time, Industry especially tends to take an interest in subjects and develop fields of knowledge which can be expected to be 'marketable' within the foreseeable future, which is to say can be expected to enable money to be made in one way or another. This is understandable: a business has to be profitable to ensure its continuity. However, it does also mean that the corporate sector will not voluntarily develop knowledge with an unlikely or uncertain 'marketability', whereas this type of knowledge could offer major benefits from the public health point of view. The public health knowledge requirement mainly

plays a role in the composition of the industrial research agenda where need coincides with commercial feasibility or the prospect of making a profit. The assumption here is that if high profits are anticipated from a given product, there will also be a major need for it from the public health point of view.

The compatibility of this commercial feasibility and public health interests is not being questioned here. The position adopted in this advisory report (and substantiated with case studies) is that the development of biomedical knowledge would be unbalanced, if knowledge development became excessively dependent on industrial research. This would also have adverse consequences for the quality of prevention and care. It is therefore in the public's interest to closely monitor the need for knowledge development from the public health point of view.

Manufacturers can affect the research agenda directly by funding research. They can also influence the research agenda indirectly, through the people who conduct the research, because companies establish endowed professorships or maintain close contact with researchers. In the case of an endowed professorship funded by a company, the professor's research is often conducted in a field in which the company has an interest, so there is a direct effect on agenda-setting for the research. A study in the Dutch daily newspaper, the *Volkskrant* (12 April 2008), showed that almost a quarter (1313) of the 5481 chairs at Dutch Universities were funded externally. Some of these involved corporate sponsoring: 27 percent of the 1313 externally funded chairs were paid for by companies.

2.2 Funding

Research funds are not only provided by industry but also government, the European Union and charitable funds, such as the Dutch Heart Foundation, the Diabetes fund, Dutch Cancer Society (KWF) and (indirectly) by the Postcode Lottery. In this sense the terms public sector (government, EU) and private sector are also used, whereby the latter can be subdivided into the non-profit sector (charitable funds) and profit sector (industry).

As a consequence of the Lisbon agreements (2000), European Union member states agreed in 2002 that they would endeavour to spend 3% of their Gross National Product (GNP) on Research & Development. A third of this has to come from public investments and two thirds from private investments. As an EU member state, the Netherlands is bound by this obligation of means. However, public investments in research and development in the Netherlands amount to only 0.7 to 0.8% of GNP, which is 0.2 to 0.3% below the agreed standard of 1%. For a GNP of 600 billion euros, this amounts to a shortfall of more than 1 billion euros, as noted in December 2008 by Professor P. Nijkamp in his parting speech as NWO chairman. His conclusion was that the Netherlands, as a respectable scientific country, is still failing to invest sufficient funds in research (see also the newspaper interview in the *Volkskrant* of 3 January 2009). However, the business sector's score is even lower, as the percentage for private investments fluctuates at around 1% of GNP instead of the 2% it ought to be.

In 2001 the fifteen EU countries spent an average of 1.98% of their Gross Domestic Product (GPD) on R&D, of which 56% was paid for by the business sector. This was well below investments in R&D in the United States and Japan. R&D expenditure in the United States was 2.72% of GDP, with the business sector accounting for 67% of expenditure, and the figure for Japan was 3.07% of GDP, with the business sector accounting for 73% of expenditure (UK Postnote 2004). All the above figures concern R&D in general.

The following applies to biomedical R&D. Expenditure on biomedical R&D in 2004 in the non-market sector was between 0.37 and 0.40% of GDP in the United States, while the fifteen 'old' EU countries spent an average of only 0.17% of GDP. The percentage in the United States is therefore more than twice as high. This background should be taken into account when considering the recommendations made in 2007 by the European Science Foundation (ESF) and the European Medical Research Council (EMRC) that public funds for medical research in Europe should be doubled within ten years, that is to at least 0.25% of GNP, with an increasing share for PPP programmes (see section 2.4) (<http://www.esf.org>).

The size of health-related R&D expenditure in the Netherlands is as follows. Total R&D expenditure in the Netherlands in 2003 was 1702 million euros, of which universities and UMCs accounted for 653 million, the pharmaceutical industry for 462 million, other industries and the wholesale trade for 254 million, research companies for 187 million and institutions other than universities and UMCs for 146 million (figures from talk by H. Smid, director of the Netherlands Organisation for Health Research and Development (ZonMw), on 1 October 2008, in Utrecht).

The government has established organisations such as ZonMw and the Advisory Council on Health Research (RGO), also with a view to achieving balanced knowledge development and promoting research into socially important topics in the field of public health and health care. Moreover, the Royal Netherlands Academy for Arts and Sciences (KNAW) and the Netherlands Organisation for Scientific Research (NWO) are responsible for fundamental or basic research, whereby the focus is on knowledge development.

ZonMw, Netherlands organisation for health research and development, provides public funds (from the Ministry of Health, Welfare and Sport and NWO) for knowledge generation in the field of health research, development and policy (<http://www.zonmw.nl>). In 2007 ZonMw subsidised projects (not only scientific research but also projects concerned with implementation) for a sum of around 155 million euros, of which around 111 million was funded by the Ministry of Health, Welfare and Sport, 35 million by NWO, and the remaining 9 million by third parties (charitable funds, other ministries). The RGO which, following its merger in 2008, is now part of the Health Council of the Netherlands, has the task of providing advisory reports for the Minister of Health, Welfare and Sport, the Minister of Education, Culture and Science, and the Minister of Economic Affairs, on priorities in health research, care research and developing new technologies in the sector, as well as on the associated infrastructure, whereby the public

health perspective is always the starting point. Setting the agenda and priorities for research is therefore an important aspect of RGO's mission and vision.

On several occasions the RGO's advisory reports have resulted in ZonMw research programmes.² Examples include the RGO advisory reports on rehabilitation (1998), public mental health and mental health care (1999), prevention (2001), infectious diseases (2003) and medical care for older people (2006). The RGO advisory reports on public health (2000-2003) resulted in a ZonMw programme for Academic Collaborative Centres for Public Health, and in nine collaborative centres. The government also adopted an RGO advisory report which presented a research agenda for medical biotechnology (2006), in which the highest priorities were a. obesity/diabetes mellitus/cardiovascular diseases, b. cancer, c. disorders of the locomotor apparatus, especially osteoarthritis.

However some RGO advisory reports had less impact, such as the RGO advisory reports on trauma care (2002) and occupational medicine (2003). There are still some knowledge 'blank spots' in the field of trauma care and occupational medicine which need to be filled from the public health point of view. A case study in a recent RGO advisory report³ confirmed a blank spot in academic research in the field of occupational medicine. Another example of a field of research with blank spots is drug research (see also RGO advisory report on the Dutch knowledge infrastructure for the pharmaceutical care sector: *Kennisinfrastructuur Farmaceutische Zorg* (2005). Some subjects were not taken up by the industry and ZonMw also paid little attention to them because hardly any assignments were granted for them. An example of this was research into the responsible phasing out of drugs, which is not compulsory for their registration.

2.3 Clinical research

In the case of the funds available for academic research a distinction is generally made between the 'first', 'second', 'third' and 'fourth' 'flow of funds'. The terms first and second flow of funds have a well-defined meaning: first flow of funds means the university budget from the Minister of Education, Culture and Science (the state grant) and second flow of funds means subsidies from ZonMw and NWO. The way in which the term third flow of funds is given shape can vary (see for example http://www.hiil.nl/nwohome.nsf/pages/NWOP_6EYCLQ and ⁴). In this advisory report we consider the third flow of funds as subsidies from ministries, the European Union and private non-profit funds (hereinafter referred to as charitable funds), and we consider the fourth flow of funds as funding by the business sector. Researchers and research institutions may also have funds at their disposal from specific legacies and donations from private individuals.

Since the mid-nineteen-eighties government has urged universities to exploit the fourth flow of funds, namely by conducting more contractual research with the business sector as the client. The first flow of funds for research has remained the same over the years or increased slightly

whereas the other flows of funding have tended to increase relatively more. Universities went in search of other sources of funding to supplement the fixed university budget. The volume of research commissioned by industry, including the pharmaceutical industry, increased; academic medical research and industrial research became increasingly intertwined.

This development is valued in various ways. The positive aspects are usually emphasised (more money and therefore more research opportunities) while recognising the necessity of assurances for the independence of the research to be conducted.⁵ Academic researchers are sometimes so successful in the cooperation with industry that they are able to implement their academic research agenda (*investigator-driven research*) with the aid of funding from the fourth flow of funds. This mainly concerns large research groups that conduct research for many manufacturers, rather than just one. Their strategy is that working in this approach enables them to prevent an individual manufacturer from exerting too much influence on their research agenda.

There are also downsides to this increased interrelatedness. There is a risk that the (relative) ease with which industrial funds can be obtained for research (not always peer review, as is the case with subsidies from ZonMw and charitable funds, less competition with colleague researchers) and the size of the fees paid by industry may carry some weight in the composition of the academic research agenda, which could detract from the attention paid to the social benefit and quality. We illustrate this below with a few examples taken from academic medical practice.

The public health benefits of some research projects commissioned by industry are questionable. A case in point is the placebo-controlled trial of the efficacy of a new drug for a condition for which several efficacious drugs are already on the market (*me-toos*⁶). Research demonstrating the added value of a new drug vis-à-vis an existing drug is much more important because it is more in line with the needs of patients and doctors (see also section 2.5). Other no less important research includes that in which pharmacological and non-pharmacological interventions are compared, or complex strategies, of which drugs may form a component, along with other medical or paramedical treatments, such as clinical diagnostics and the use of diagnostic technology, surgical and obstetric techniques, rehabilitation methods and psychotherapeutic interventions. This may also involve protocols built up step by step or guidelines which may include diagnostic, therapeutic and follow-up elements. Generally beyond the scope of industrial sponsoring, clinical research of this kind is necessary throughout health care. And because it frequently concerns more than one possible condition, it often fails to qualify for funding by charitable funds. Public funding, through the budgets of university medical centres or otherwise, is therefore vital here. However, the large size of this field of research makes it necessary to create additional sources. The fact that this is beginning to be seen internationally too is illustrated by the recent initiative of the United States government to give *comparative effectiveness research* a major financial injection (see concluding section 4.2).

The high payments manufacturers make for each patient included, sometimes amounting to thousands of euros, may be an additional problem. Whether or not the size of the payment is acceptable depends on issues such as what has to be done in aid of the research. For example, a research nurse must sometimes be appointed. Patients are generally unaware that a particular payment is being made for their participation. The fact that payments for one trial may be much higher than for another for no apparent reason is a thorny issue. In such cases there is a danger of the size of the payments determining whether the research is conducted, rather than the need from the public health point of view. In fact the practice is that the field displays a great deal of interest in conducting trials involving the highest payments. Trials addressing a meaningful or more meaningful question but which pay much less per patient are less likely to get off the ground.

The above examples also raise the question as to which research patients may be exposed. Is it ethically responsible to ask patients to participate in research that is of secondary importance to public health, for example placebo-controlled *me-too* trials? This also involves the professional ethics and integrity of the individual researchers. They could refuse to work on *me-too trials* to which they did not wish to expose patients because they could not see the benefit of doing so. Besides placebo-controlled trials, comparative research can also be ethically problematic. If the new drug is no better and at best just as good as an existing drug, also with regard to side-effects, should subjects/patients be exposed to it? The fact that such an objective is accepted in aid of registration does not necessarily mean that it is ethically acceptable. And would the acceptability change if it could be demonstrated that *me-too* preparations made drugs cheaper?

It should be noted here that in the Netherlands scientific and ethical appraisal of medical research involving human subjects is subject to the regulations of the Medical Research (Human Subjects) Act. Research of this kind should be able to meet the scientific and ethical requirements of either a recognised Medical Ethics Review Committee (METC) or the Central Committee on Research Involving Human Subjects (CCMO). These committees only provide a positive assessment if it is 'reasonably plausible that the scientific research will lead to new medical insights' (section. 3, subsection a, WMO). This is therefore concerned with new scientific insights. The burning question is whether this can also be deemed to include making drugs cheaper.

Questions may also arise from the point of view of corporate social responsibility regarding the use of the – by definition limited - number of prospective subjects/patients. University hospitals conduct so much research that they almost have a shortage of patients. It is even more important to get the priorities right in such situations, whereby not only the scientific interests but also society's interests are important. Research capacity is by definition limited and can only be deployed once, and the time of doctors/researchers is particularly expensive. University Medical Centres have three main tasks: care, research and education/training. This could also lead to tension in the endeavour to provide good care.

Practically all the university hospitals have developed research codes in recent years to clarify the border between authorised and unauthorised treatment and between responsible and irresponsible treatment in the field of clinical research. Most general hospitals have no such codes yet these hospitals also conduct research commissioned by the business sector. The greatest likelihood of dubious research (*me-too trials*, seeding trials (covered in section 3.4)) exists where no strong research infrastructure has been developed. This is more likely to be the case in general hospitals and general practices than in university hospitals, although clinical research on those sites is also subject to review by METCs*.

Essential questions concerning the composition of the research agenda are therefore: where do the priorities of a doctor/researcher and patient lie and which parties influence the priorities? To what extent is this affected by motives such as the ease of obtaining research contracts and financial considerations (income for the research group, higher individual earnings)? From the public interest point of view, which subjects should be high on the agenda but frequently have a lower place because other matters are given priority? And the key question: what can be done about this?

2.4 Public-Private Partnerships

A Public-Private Partnership (PPP) is a type of cooperation between public sector and the private sector, in which the two sectors carry out projects jointly. The intention is that by combining their strengths the two sectors can achieve more and better results than through working separately. A strong point of the business sector is that it generally has market insight and investment opportunities at its disposal, while government has a good idea of public health requirements. In the field of medical research PPPs can prove their value internationally, for example in the development of priority medicines. PPPs are also suitable for bridging the gap between fundamental research and applied clinical research (translational research) because partnerships like these enable knowledge and expertise acquired in the individual sectors to be exchanged, which can give knowledge development and implementation new impulses.

The Dutch government encourages public-private partnerships, by, for example, providing funds from the Economic Structure Enhancing Fund (FES). This fund (around 40 percent of natural gas revenues) is for strengthening the infrastructure in the Netherlands, including the technology and knowledge infrastructure. The incentive mainly focuses on parts of the infrastructure in which the Netherlands has a good starting position from the international point of view. The idea is this is where major innovative and economic successes can be achieved in due course for little extra investment.

* However, phase IV research is not always covered by the Medical Research Involving Human Subjects Act. Phase IV research not covered by the Medical Research Involving Human Subjects Act is not subject to METC or CCMO review. Also see the footnote in section 3.4.

Examples of PPPs in the Netherlands include Top institute Pharma (TiPharma, drug research, <http://www.tipharma.com>), BioMedical Materials programme (BMM, development of new bio-medical materials and their application, <http://www.bmm-program.nl>), Centre for Translational Molecular Medicine (CTMM, development of medical technology for early diagnosis and new patient-specific treatments for severe diseases, <http://www.ctmm.nl>), Top Institute Food and Nutrition (TiFN, development of innovative food products and technologies, <http://www.tifn.nl>) and (in formation) Top Institute Grow Old Healthily (Ti-GO, science and technology for growing old healthily and being an active participant in the community for longer, <http://www.ti-go.nl>). Researchers from universities, academic centres and large companies work together through these links. ZonMw also encourages and increasingly uses PPP-like constructions, in connection with disease management, for example.

In terms of the economic aspect, research can roughly be divided into three types:

- Research that is certain to be financially lucrative (some of the research into new drugs, for example)
- Research which has a chance of producing economically valorisable results
- Research that is certain not to produce commercially marketable results, such as much of the research into collective public health interventions.

PPPs mainly conduct research into the second type. In the first type of research there is no direct need for public-private partnerships because the research is taken up adequately by the business sector. The last of the aforementioned types of research is unsuitable for the PPP model because companies are generally unwilling to invest time and money in it.

Is it acceptable for government to use public funds for research which is not certain to be economically valorisable? This seems just as acceptable as investing in research that will never be valorisable, provided it concerns knowledge development that serves a public health interest. It is essential that clear agreements are concluded beforehand about the division of revenue, if the developed knowledge can be made financially lucrative. It is reasonable for part of the revenue to flow back to the public domain, in proportion to the government investment. It is therefore important to ask what agreements were made about this at the commencement of the PPPs.

2.5 Case study: drug research

The WHO report *Priority medicines for Europe and the World* (2004)⁷ identified 'gaps' in drug research and the associated innovation and identified seventeen conditions which should either be paid more attention to in drug research or for which prevention is especially effective. Drug development for specific groups of patients and for developing countries should be given precedence. The European Union and European Medicines Evaluation Agency (EMA) have started to flesh out the research agenda for this. ZonMw is also working on this (see below). TiPharma's research agenda was also determined under the influence of this WHO report.

Drug development is the pharmaceutical industry's *core business*. In the sections below we examine which drug research the manufacturers are willing to fund on the basis of this mission and which research they are not willing to fund. This enables us to identify knowledge gaps.

When new drugs come onto the market, it is often not known whether they work better than the drugs which are already on the market

Until recently, when a new drug came onto the market, in more than half the cases we only knew that it was more efficacious than a placebo. We had no knowledge of whether it was more efficacious than the standard treatment; in other words it was not known whether the drug actually signified an improvement for patients.⁸ This did not apply to drugs such as those for treating cancer and cardiovascular diseases, as the research in aid of registration was always required to compare them with the standard treatment because it would be unethical to withhold treatment from severely ill patients. If at all possible, for the registration of a new drug, manufacturers will tend to limit their research to a placebo-controlled trial, because this is more likely than a comparative study to lead to significant results. A comparative study conducted after the new drug's registration is often necessary to determine whether the new drug is actually better. However these studies are frequently not conducted.

What are the possible consequences of this for patients? It may mean that they are given less efficacious or less safe drugs than necessary.

The fact that drug research was or still is often placebo-controlled calls into question the acceptability of this situation. Guidelines exist on the acceptability of placebo and 'no treatment' approaches in drug research. It is assumed in article 29 of the *Declaration of Helsinki* (2000) that a new method of treatment should in principle be compared with the best (preventive, diagnostic, therapeutic) method available. The article only permits placebo or 'no treatment' approaches if no proven efficacious method is available. In an explanatory note to the article of 2002, the World Medical Association (WMA) named the types of circumstances in which a placebo-controlled trial may be ethically quite acceptable when proven efficacious treatments are available, for example when there are good methodological reasons for using placebos. In 2002 the CCMO confirmed that sound scientific reasons may exist for using placebos in clinical utility studies.⁹

The WMA's explanatory note was clarified in 2008 and included in the text of the *Declaration*. The article concerned (32) now reads as follows: *The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:*

- *The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or*
- *Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.*

The starting point for the EMEA, the European Medicines Agency, is *ICH Guideline E10 on the 'Choice of control group and related issues in clinical trials'*. This guideline is one of the many drawn up by the International Conference on Harmonization (ICH) with the intention of providing a basis for the format of drug research that is part of a registration dossier. The Efficacy Working Party (EWP) of the Committee for proprietary medicinal products (CPMP), which is part of EMEA, also drafted guidelines specifically intended for certain classes of disorders, such as for the treatment of depression, hypertension, heart failure and epilepsy. The various guidelines of the CPMP and ICH contain all kinds of variants for research formats in which a placebo group may be acceptable when a proven effective therapy exists.⁹

According to the registration authorities, the clinical utility of new drugs can indeed sometimes be demonstrated without placebo-controlled trials. However, they believe placebo-controlled trials are essential in other cases.¹⁰ (See also <http://www.cbg-meb.nl> under the headings Human Medicines, News, Overview, 25 February 2008 – Why placebo if there is an active treatment available?) According to CPMP it is not in the interest of patients to always require that the new drug must be found to be more effective than the standard treatment (*superiority trial*) because this would impede the marketing of new drugs that are just as effective as existing drugs but have fewer side-effects. One alternative to the *superiority trial* is the *non-inferiority trial*, which is a trial in which it is attempted to demonstrate that the new drug is just as effective as (or equivalent to) the standard treatment. The CPMP points out that *trials* of this kind are intrinsically less reliable than superiority trials.¹⁰ The fact that such a trial shows that the new drug is equivalent to the standard treatment does not demonstrate that the new drug is also actually effective. The observed effect could also be the result of the condition taking its natural course. To provide a definite answer the two 'arms' of the study are supplemented with a third 'arm' in the form of a placebo group. It can be concluded that the new drug is not effective if the effect in the placebo group is equivalent to that in the two groups receiving treatment. However, if the effect in the placebo group is less than that in the treated groups, it may rightly be concluded that the new drug contains an active ingredient.

Given the limited availability of trials in which a new drug is compared with an existing effective drug, while such a trial should be the rule when a proven effective treatment is available, the question arises as to whether registration authorities in the recent past have provided too many opportunities for placebo-controlled trials. It was with good reason that the World Medical Association included the warning in the *Declaration of Helsinki* that extreme care must be taken to avoid abuse of the second exception. EMEA and CPMP have become clearer in their guidelines over the years: for registration they increasingly ask for research conducted using an *active comparator*.

Moreover, in the situation in the Netherlands, a drug which is on the market only qualifies for payment following a recommendation by the Committee for Pharmaceutical Help (CFH) of the Health Care Insurance Board (CVZ). The CFH's assessment is primarily based on comparative research (comparison with existing drugs). Consequently, a drug only qualifies for payment if it is just as good or better and just as safe or safer than an existing drug. In short, if only placebo-controlled trials are available when suitable drugs exist, the drug will often not

qualify for payment. This is a major incentive for the pharmaceutical industry to conduct comparative research.

The patient population studied usually includes only relatively healthy middle-aged people

Another knowledge gap relates to the fact that trials in phase 3 (that preceding registration) are often conducted in relatively homogeneous groups of middle-aged subjects without comorbidity.* It is often not known at the time of registration whether and to what extent a drug works for people with more than one chronic disorder or for people who are taking several medicines at the same time, or for children, adolescents and elderly people.

Registered new drugs are nevertheless prescribed for patients in these groups. Additional trials are sometimes conducted in these groups when a drug has been on the market for a number of years. However, this is also selective. The pharmaceutical industry does not conduct trials with these groups; this is also in connection with the ethical complexity of doing so, the perceived risks and/or subjects' incapacity.

In general practice medicine there is a major need for knowledge of effects/side-effects of medicines in a patient group which is far more representative for general practice than the group in which phase-3 trials are usually conducted, especially in the case of patients with multimorbidity (see Health Council's advisory report no. 2008/01 *Health care for the elderly with multimorbidity*). The inclusion criteria for clinical trials conducted in aid of registration are only met by a small percentage of the patient population in primary health care. For example, the figure for studies of the clinical utility of medicines for heart failure is only 13 to 25 percent. Little is known about the interaction of drugs that are often used in combination, such as statins and chemotherapy, yet this knowledge is of major importance for medical practice.

Medicines prescribed for children are not always tested on children

Drug research involving children is an example of a field that has long been neglected (see also chapter 3, Medicines for children, in: Ethics and Health Monitoring Report 2003¹¹) but which has begun to receive more attention in recent years within the scope of priority medicines. The importance of research of this kind is clear from, for example, the discussion revolving around the frequent use of a certain type of antidepressant drugs, the SSRIs, by children. Although the efficacy and safety of these drugs had not been adequately proven for their use by children, they were nevertheless widely prescribed for children.¹²⁻¹⁴ The drugs increased the risk of suicide, a side-effect of which the manufacturer was aware but had withheld information.^{15,16} The new EU Directive stipulates that trials involving children must be conducted before a new drug can be registered for use by children. To encourage industry to

* However, there are good methodological reasons for conducting phase-3 trials in tightly controlled groups. In clinical utility studies it is advisable not to incorporate too many variables (age, comorbidity, comedication, etc.) as doing so would only reduce the *power* of the study. Research conducted with specific patient groups is often separate research. Methodologically a tiered approach of this kind is better than a large trial with many variables/confounders. The effect in daily practice can be studied in a later phase (phase 4).

conduct more trials involving children, it has been decided that the patent on a drug will be extended by six months if the results of a trial involving children are submitted to the registration authority at the time of registration. The hope is that this approach will gradually close the knowledge gap.

In this respect it is extremely important that this leads to research into the clinical utility of drugs which are actually needed in paediatrics. This has thus far not been the case: industry has mainly involved children in trials to test drugs that were promising from the marketing point of view (antidepressants and mood stabilisers, drugs to reduce cholesterol levels, etc.).¹⁷ The new EU Directive cannot help with the lack of knowledge on the efficacy and side-effects in children of existing drugs that have already been registered.

In the Netherlands, scientific research involving children is also subject to statutory restrictions. Scientific research involving minors is prohibited unless the research can benefit the children involved or unless the research can only be conducted with their cooperation, involves negligible risks and the objections to it are minimal (section 4, subsection 1, WMO). The Doek Committee, a committee established by the Ministry of Health, Welfare and Sport and the Ministry of Justice, is currently examining the extent to which it would be advisable to broaden the present scope for conducting medical research involving minors when the results cannot benefit the subjects (non-therapeutic research). This involves finding the right balance between, on the one hand, protecting minors participating in trials and, on the other hand, increasing knowledge of their prospects for treatment. The Doek Committee intends to present its advisory report to the Minister of Justice and the State Secretary for Health, Welfare and Sport at the end of 2009.

The *Medicines for Children Research Network* (MCRN) was set up in 2008. The network will promote the coordination, quality and pace of research into medicines for children and adolescents. The network receives financial support from the Ministry of Health, Welfare and Sport, the Netherlands Federation of University Medical Centres (NFU) and various large pharmaceutical companies (<http://www.mcrn.nl>). The network has modest funds, although the government provided a substantial financial contribution for its establishment.

Little is known about long-term effects

Knowledge about the long-term effects of drugs is also absolutely insufficient. Drug research is usually short term (6 to 12 weeks). The follow-up period for research into drugs for chronic conditions is often limited. We frequently know nothing of the side-effects after one or more years of use.

It is extremely important for research into the clinical utility of new drugs to use clinically relevant outcome measures, such as morbidity, mortality and quality of life. However, in drug research in aid of registration, intermediate end points are often found, such as blood pressure, blood sugar level, and cholesterol, which may or may not be clinically relevant. Some-

times there is no alternative, such as for a condition for which no other treatment currently exists, when the effects of a drug can only be expected after a very long period and the effects at the intermediate end points appear promising. In such cases this does not release the manufacturer from the responsibility of demonstrating the ultimate effects on the basis of concrete outcome measures, if necessary after introduction to the market.

The fact that a new drug has been registered for use for a particular indication does not therefore mean that efficacy has also been demonstrated at clinically relevant end points. The example of the *me-too* rosuvastatin is illustrative of this. This drug came onto the market in the Netherlands at a time when four other statins had already been registered. A year after rosuvastatin was placed on the market, the CBG clarified the product information, owing to the occurrence of a severe side-effect. Two years after market introduction, a search for rosuvastatin in Pubmed revealed forty Randomized Controlled Trials (RCTs) which only included surrogate and laboratory parameters, and no clinical cardiovascular end points. Nevertheless, doctors frequently prescribed the drug as a result of effective marketing (*Geneesmiddelenbulletin* 2005 (July), 39, 83-84).

Another area in which we often find ourselves in the dark concerns the effect of a given medicine vis-à-vis a disorder's natural course: what is the outcome over time for people who receive no treatment in comparison with those who receive treatment? Long-term research of this kind is difficult and expensive. It can also be ethically problematic because a group of patients has to forgo treatment for a long period. Moreover, it is difficult to finance if there is little interest in it for the industry.

The latter also applies to research into the responsible phasing out of drugs, especially in situations involving cumulative polypharmacy. The ZonMw programme Priority Medicines for the Elderly addresses the subject of polypharmacy and multimorbidity.

Little is known about side-effects

Drug research should pay more attention to research into severe side-effects than has been the case thus far in *Post Marketing Surveillance* (PMS). In the first few years after a new drug's registration there are often many gaps in what is known about its side-effects; the clinical trial model is not especially suitable for identifying side-effects that occur less frequently. When a new drug comes onto the market its efficacy has generally been determined through trials involving a few thousand patients. The most frequently occurring side-effects are known by then. However, some severe, less frequently occurring side-effects only come to light after the drug's registration when its use is widespread. Over the past decade, ten to fifteen drugs have been taken off the market because they proved to have unacceptable side-effects (cardiac abnormality and so forth). These included COX-2 inhibitors, such as rofecoxib (Vioxx) and valdecoxib, cerivastatin and various antibiotics. The indication for many drugs has been clarified or the precautionary measures in the product information have been clarified, so that

fewer people qualify to be prescribed it (new antidiabetics such as rosiglitazone and pioglitazone, and other COX-2 inhibitors).

Special attention should be paid to side-effects that only occur in the long-term, which means after ten to twenty years, and which can therefore only be identified after many years. Such side-effects are not necessarily uncommon. An example of this is the occurrence of damage to the heart caused by anthracyclines in chemotherapy. *Post Marketing Surveillance* should therefore cover a period of ten to twenty years after a drug has been placed on the market.

For several years now, EU regulations have obliged manufacturers to provide the registration authority with a *Risk Management Plan* when submitting applications, especially in the case of medicines containing a new active ingredient. The obligation is intended to increase the likelihood of detecting side-effects, rare or otherwise.

Manufacturers sometimes make little effort to change off-label use into registered use

Sometimes it is not sufficiently in the interest of a manufacturer to register a drug for a given indication, so no research is conducted into the drug's use for that indication and doctors continue to depend on *off-label* use for the indication concerned. This applies for example in the case of the drug misoprostol (Cytotec). The manufacturer only registered the drug as a gastric protector but in practice it proved to be efficacious in countering continued bleeding after childbirth, pregnancy termination and accelerating the completion of miscarriages. As such, the drug has an important function in obstetrics.¹⁸⁻²⁰ Doctors who wish to use the drug for these indications are required to state in the *informed consent* procedure that it is being used *off-label*. An inherent part of such use is that no research, industrial or otherwise, is conducted that meets the clinical utility and safety requirements stipulated by the registration authority for use of the drug for a given indication. Funding from a non-industrial source is necessary to get clinical trials off the ground that would meet the requirements.

Few trials of competitive, cheaper drugs

There have also been few trials of long-established or novel, cheaper drugs which appear promising according to individual experiences of doctors or patients but which may compete with drugs that are already on the market. Long-established drugs for which trials are no longer conducted include tuberculostatics. Closer study of the kinetic-dynamic relationship and mechanisms of side-effects could possibly enable these drugs to be used more effectively and safely. However, manufacturers do not carry out this type of research. Research of this kind therefore depends on government funding.

Few trials of compliance

Efficacy at clinical end points has been convincingly demonstrated for many drugs that have been on the market for longer. Nevertheless, large groups of patients either do not take these drugs or take the wrong dose. The reason for this is unclear. Is this attributable to the doctor, the patient, or how health care is organised? More research into therapy compliance could

provide clarity about this, so that the intended use of the drug could be promoted more effectively. Pharmacists could help pay for this research because they also have an interest in proper use.

Research to be subsidised by ZonMw

ZonMw is currently attempting to fill some of the aforementioned gaps in drug research. The initiatives are summarised below.

Following on from the WHO's report on priority medicines⁷, ZonMw has submitted four proposals for research programmes to the Ministry of Health, Welfare and Sport since 2006:

- Priority Medicines for Children
- Priority Medicines for the Elderly
- Priority Medicines for Antimicrobial Resistance
- Priority Medicines for Rare Conditions and Orphan Drugs.

The state of affairs regarding these proposals is as follows. The programmes *Priority Medicines for Children* and *Priority medicines for the Elderly* started in 2009. The programme concerning antimicrobial resistance will start in late 2009. The strategic research programme concerning rare conditions and orphan drugs still has to be commissioned by the Ministry of Health, Welfare and Sport.

ZonMw also presented advisory reports to the Ministry of Health, Welfare and Sport, on for example *fixed dose combination*, but this has thus far not resulted in any definite commission from the Ministry of Health, Welfare and Sport. In the summer of 2008 ZonMw conducted inventory studies of a total of eight diseases, likewise in response to the WHO report on priority medicines. The studies were combined in two reports. The diseases were pandemic influenza, Alzheimer's disease, chronic obstructive pulmonary disease (COPD) and arthrosis, and HIV/AIDS, tuberculosis, *neglected diseases* and malaria. The reports include numerous recommendations for research.

In early July 2009 ZonMw presented the Ministry of Health, Welfare and Sport with the advisory report on the proper use of medicines ('Goed gebruik van geneesmiddelen'). The advisory report includes recommendations for tackling the knowledge gaps in drug research. The proper use of medicines is concerned with using registered drugs effectively, safely and efficiently. ZonMw hosted an *invitational conference* concerned with this on 24 September 2008. Participants made an interim assessment of drug research in the Netherlands. The main conclusions were presented in the advisory report. Participants were of the opinion that a lot of gains could still be made in the area of the proper prescription and use of drugs. Targeted scientific research in four areas could result in better treatment for patients:

- Are drugs prescribed when necessary?
- Is the right medicine at the right dose prescribed?

- Can the drug be used for other indications and is this done?
- Is the drug used properly?

The Minister of Health, Welfare and Sport has indicated that he also sees improving the use of medicines as an innovation, all be it a different type of innovation from the discovery of a new drug. After all, the impact on care could be just as great. The minister seeks to set priorities in cooperation with the Ministry of Education, Culture and Science and the Ministry of Economic Affairs.

Conclusion

The conclusion is that knowledge of drugs is limited and will probably remain so, if we leave its development entirely to the pharmaceutical industry:

- Research is still hardly ever conducted that has little prospect of valorisation, such as research into drugs for rare diseases or research into the responsible phasing out of drugs
- When new drugs come onto the market, it is often not known whether they work better than the drugs which are already on the market
- In many cases there is a lack of research into the efficacy of new drugs among groups composed of children, adolescents, elderly people or patients with multimorbidity, for example
- Little is known about the long-term effects of drugs. At the time drugs are placed on the market their efficacy at clinically relevant endpoints has often not yet been demonstrated
- *Post Marketing Surveillance* by manufacturers is too limited (long-term clinical utility, infrequent and/or late side-effects)
- Manufacturers sometimes make little effort to change *off-label* use into registered use
- Once a new drug has been registered, there is often a lack of follow-up research, also known as *outcome research*. Research of this kind is essential for determining the new drug's actual value in daily medical practice. There might be an important task here for drug research paid for by public funds or public-private funds
- Initiatives have been taken to close the gaps in drug knowledge, for example:
 - WHO report *Priority medicines for Europe and the World*
 - ZonMw's development of the theme concerned with the proper use of medicines
 - Establishment of the Medicines for Children Research Network (MCRN) with support from the industry, amongst others.

2.6 Case study: research into diagnostic devices

The terms 'diagnostic' and 'diagnostic devices' are ambiguous. A distinction is made between various diagnostic categories in the background study to this advisory report:

- pre-diagnostic processes/devices, such as prenatal and genetic tests
- anamnesis (i.e. case histories), physical examinations and instruments, such as those used for blood tests, that enable doctors to make the usual clinical diagnosis as part of compiling the case history

- secondary diagnostic devices, such as imaging technologies, scopes, scanners, laboratory tests, and certain function tests, such as the cardio stress test
- devices for monitoring (following a particular treatment's progress for a patient)
- new diagnostic devices, such as genetic tests based on a mouth swab, and total body scans
- all kinds of do-it-yourself tests.

Moreover, there is a lack of clarity about the distinction between a diagnostic test and a biomarker, which can be used for disease identification and monitoring, so the collective term 'diagnostic devices' is also used in relation to biomarkers.

The collective term 'diagnostic industry' is used to refer to a large, fragmented whole with an extremely diverse composition. It includes multinationals such as Philips, Siemens and Johnson & Johnson, but also a growing number of small and medium-sized enterprises producing a variety of devices for health care technology. It involves a segment of the market which is developing rapidly.

While stringent statutory rules apply to marketing new drugs in Europe, this is much less the case for diagnostic instruments.²¹ At most, EU regulations oblige manufacturers to guarantee that the devices or processes concerned really do measure what they purport to measure and that they are safe to use, which means that they will not cause any direct physical harm to the people using them. The rules on these instruments in the United States are generally stricter than those in the European Union. Barring a few exceptions, EU regulations contain no clear obligation for the manufacturer to submit proof of the diagnostic validity and clinical benefit of the diagnostic instrument. It is often unclear when a test of this kind comes onto the market whether patients will actually benefit from its use and whether its use is cost-effective.* Practitioners or hospitals wishing to make use of given diagnostic devices often have to conduct their own reliability tests. This is usually not done owing to a lack of financial and other resources. Consequently, substantiation of the diagnostic instrument's efficacy and cost-effectiveness is often inadequate. Moreover, many diagnostic methods and technologies are not interesting for the 'market' but are extremely important for daily practice, such as case histories, physical examinations and simple, additional blood tests. Hardly any funds are available for studies of the validity of this range of such important instruments.

Using a suggestion made by one of the interviewees within the scope of the background study, to enable comments on the development of the research agenda, it may be helpful to divide the development process of diagnostic instruments into different phases.

The first phase is concerned with the development of the actual product. The manufacturer clearly has a great deal of influence in this phase. Some initiatives for innovations are taken

* On the other hand, manufacturers wishing to have their product included in the basic health service entitlement package must be able to demonstrate its clinical utility and cost-effectiveness.

from the scientific sector. Examples of this in the field of screening include the HPV DNA test for cervical cancer and the PCA3 test for prostate cancer.

The second phase is concerned with evaluating the instrument. There is a major need in this phase for additional research, publicly funded if necessary, at least for as long as legislation sets so few requirements and manufacturers do no more than what is statutorily required of them, which is usually the case. In addition to research conducted by general hospitals/university hospitals, cooperation between industry and universities of technology could be considered during this phase. Cooperation of this kind is already underway in Delft, Eindhoven and Twente. The manufacturer's overall influence decreases during this phase and the agenda is mainly determined by researchers.

The third phase is concerned with the instrument's implementation. This is the joint responsibility of insurers, hospitals and medical practitioners. Research may be necessary during this phase too. In this phase the research agenda is determined by the parties responsible for taking decisions.

There are currently no research programmes in the Netherlands that encompass the entire process outlined above. The *Centre for Translational Molecular Medicine* (CTMM) aims to establish such a programme but attention is currently mainly focused on the development phase. The same applies to the NWO programme 'New instruments for health care'. We must also realise that the theory and methodology of the evaluation of diagnostics still lag behind research into the clinical utility of treatment. Research into the clinical utility of medical tests is often more difficult to set up than research into medical treatments, partly because of the often indirect relationship between a test benefit and a health benefit.²¹ Difficult methodological issues include the lack of a *gold standard* (an uncontested standard used to calibrate new diagnostic tests), the complexity of diagnostic strategies, conclusively demonstrating the added value of new methods vis-à-vis existing practice, and selecting the right control conditions for this. Diagnostic research is extremely complex and involves the influence of diagnostics on the prognosis, including the effect of therapy.²² This applies all the more so to differential diagnostic research, in which more than one disorder has to be taken into account, especially in the case of aspecific complaints with a large 'problem space', such as fatigue or listlessness.

From the point of view of the importance to public health, in every phase of development of diagnostic instruments there is a need for research that goes beyond simply examining their safety, especially in the case of research into the diagnostic validity and clinical benefits of the instruments. Research is also required into the health care significance of the use made of the instruments. This requires larger investments in *Post Marketing Surveillance*. On the one hand, more quantitative research is necessary to provide better substantiation of the efficacy and cost-effectiveness of the instruments, while on the other hand there is a need for qualitative research to evaluate individual experiences of those who use the instruments.

Few funds are generally available for research into diagnostic devices and the diagnostic process. According to one of the interviewees it is difficult to obtain funding for diagnostic research, not only from industry but also from charitable funds. Experience has shown that these funds are preferably spent on preventing and treating pre-selected diseases. Moreover, differential diagnostic research often concerns a large number of possible disease outcomes. The professional groups should also do much more to develop quality criteria for diagnostics. If hospitals already provide funding for research into diagnostics, they only do so on a limited scale. Research into diagnostics and diagnostic devices largely depends on public funding.

Diagnostic research could also benefit from recent initiatives to bring together knowledge and experience from industrial and academic researchers. A few important new developments in this area are mentioned below.

A Public-Private Partnership was established which operates in the field of diagnostics, namely the *Center for Translational Molecular Medicine* (CTMM). Its mission is to develop medical technology that enables accurate, early diagnosis and new individualised treatment of severe diseases, such as cancer, cardiovascular diseases, neurodegenerative diseases (Alzheimer's disease), and infectious diseases and auto-immune diseases. Participants include universities/UMCs, medical technology manufacturers (especially Philips), chemical companies and drug manufacturers. The centre is at Eindhoven University of Technology. The Dutch government supports the initiative by making a substantial contribution from the Economic Structure Enhancing Fund (FES). Charitable funds such as the Dutch Heart Foundation, Dutch Cancer Society (KWF) and the Dutch Alzheimer Foundation also provide support. The centre's first nine projects started in 2008 (combined budget: 150 million euro (<http://www.ctmm.nl>)). The next series of projects (with the same budget) can start during 2009.

In October 2008 NWO announced phase one of a start-up programme 'New instruments for health care' (<http://www.nwo.nl/nig>). Funds totalling 9 million euros have been provided for the research programme (of which a sum of 3 million has been earmarked for R&D for instruments that contribute to safe extramural care). The start-up programme focuses on R&D for developing innovative equipment and devices for promoting health, prevention, diagnostics, prognostics and treatment of diseases and people with a disability. The key aim is to encourage development of new health care instruments (care products) that also generate new activity, employment opportunities and prosperity (economic products).

The purpose is to provide a major impulse to fundamentally strengthen the knowledge infrastructure in phase 2. The intention is to establish *Centres of Excellence* in the Netherlands in which science, companies and health care are integrated in public-private partnerships and work together systematically to accelerate the innovation and application of new medical instruments. Twenty-four ideas were submitted for centres of this kind in early 2009. Support for this initiative has been identified in the research field. The next step should be to establish

a national 'Vision on the R&D structure for new instruments in health care' in 2010, according to a combined *top-down & bottom-up* approach (further details at <http://www.nwo.nl/nig>).

Within the scope of the Health Care Efficiency Research programme, ZonMw subsidises research into the cost-effectiveness of diagnostic interventions ((see <http://www.zonmw.nl/nl/onderwerpen/werpen/alle-programma-s/doelmatigheidsonderzoek/de>).

In the autumn of 2009, RGO began processing a request for an advisory report from the Ministry of Health, Welfare and Sport concerning a Medical Products Research Agenda (drugs, biotechnology products and medical instruments). The aim is to complete the advisory report in 2010.

Publication of the WHO final report on the *Priority Medical Devices project* is expected in 2010 (http://www.who.int/medical_devices/access/en/). The report will indicate priorities or preferred directions for the development of medical instruments from the point of view of public health and health care. Countries affiliated with the WHO will then be able to use the research agenda as a basis for their work over the coming years.

Several advisory reports of the Health Council of the Netherlands referred to the major importance of research into the diagnostic validity and clinical benefit of diagnostic tests using body material. Numerous tests using body material are currently marketed which have not been demonstrated to have any diagnostic validity and clinical benefit. Manufacturers could be obliged - at the EU level - to produce evidence of a test's validity and benefit before marketing it. This would provide major incentive for industrial research into diagnostic devices of this kind.

The conclusions are as follows:

- Research into diagnostic devices lags behind therapeutic research
- The methodology for this research is more complex than that for research into treatment
- Most of the focus in research into diagnostic devices is on innovative technology.
Research into the validity and cost-effectiveness of existing routine diagnostics, such as case histories and physical examinations, is almost non-existent
- European rules for marketing diagnostic devices are less stringent than rules for marketing medicinal products
- Funding is relatively limited for research into diagnostic devices, especially for the evaluation of clinical effects
- Initiatives are also starting to fill the gaps in this area, such as:
 - CTMM
 - NWO programme: New instruments for health care
 - ZonMw programme: Health Care Efficiency Research
 - WHO's Priority Medical Devices Project.

2.7 Case study: nutritional research

Although nutritional research also covers food technology (research into food aroma, colour and taste, for example), the term nutritional research is only used here to refer to research into how foods and their ingredients affect health. Nutritional research of this kind differs from drug research, although the boundary between medicines and foods is becoming increasingly blurred by the marketing of functional foods*. Drug research produces new compounds, either synthetic compounds or natural substances that the producer has recently discovered. The producer obtains the patent on the compounds and can charge a high sale price for them for the duration of the patent, thereby recouping research costs. Conversely, foods and their ingredients have long existed and been known about, at least partially. The effect of these compounds on health still has to be established. This is an expensive and difficult process. There are few prospects for patenting as the actual compounds are not novel. It is difficult to protect investments in research into the health effects of foods. The food industry is not generally inclined to make major investments in research of this kind.

Nutritional and health claims

Under the regime of new EU legislation, as of 2010 vague health claims, such as '... aids our natural resistance', will no longer be permitted. References to disease prevention, such as 'eating ... prevents prostate cancer', are only permitted if such an effect has been conclusively demonstrated. This is because European Regulation 1924/2006 on nutrition and health claims made on foods entered into force on 1 July 2007. The regulation harmonises the rules on nutrition and health claims laid down nationally by EU member states. In the Netherlands, the regulation has been incorporated in the nutrition labelling for foodstuffs decree (Warenwet-besluit voedingswaarde-informatie levensmiddelen).

The *European Food Safety Authority* (EFSA) is working on a list of permitted claims which should be completed in 2010. EFSA advises the European Commission on whether a claim should be permitted. Many of the claims EFSA has already assessed resulted in advice against authorisation (<http://www.efsa.europa.eu>). It remains to be seen whether EFSA's assessment will encourage industrial nutritional research.

Agenda-setting and funding

The main financiers of nutritional research in the Netherlands are the food industry and, in the case of government funding, the Ministry of Economic Affairs. Other financiers include the European Union, ZonMw (the Ministry of Health, Welfare and Sport, NWO), NWO (Ministry of Education, Culture and Science), the Ministry of Health, Welfare and Sport and the Ministry of Agriculture, Nature and Food Quality, and charitable funds. An outline of the types of research that are funded and by which parties is provided below.

* *Functional foods* are foods with added ingredients which are claimed to promote health.

Basic research

Basic, precompetitive nutritional research in the Netherlands is largely funded by the *Top Institute Food and Nutrition* (TiFN), in Wageningen ([http:// www.tifn.nl](http://www.tifn.nl)), a Public-Private Partnership in which academic researchers from Wageningen, Maastricht and Groningen, research institutions such as the Netherlands Organisation for Applied Scientific Research (TNO), the Netherlands Institute for Health Services Research (NIZO) and the food industry work together. TiFN's main sponsors are the Ministry of Economic Affairs and various food manufacturers (TiFN Annual Report 2007). TiFN's budget in 2007 was more than 25 million euros, of which more than 6 million came from industrial partners. An example of basic nutritional research is *nutrigenomics*, which studies the interaction between nutrition and genes. Industry has a significant say in the composition of TiFN's research agenda, while government, especially the Ministry of Health, Welfare and Sport has little, if any, involvement (*Background study*, page 17). Research conducted by food manufacturers is concerned with subjects such as patentable food ingredients, for example yoghurt bacteria. Dairy products containing such patented bacteria account for part of the *functional foods* market. It has not been proven that these products promote health.²³

Application-oriented research

The European Union also funds a great deal of nutritional research. This is more concerned with application-oriented research than basic research. Applications for research funding within the scope of an EU Framework Programme have to be made in cooperation with the business sector, and a plan has to be submitted containing ideas on how the research results will lead to novel, commercially interesting products. Industry can exert a great deal of influence on setting the agenda for the subjects. EU funds have been and are still used to fund various types of nutritional research, such as research into micro-nutrients, obesity and fatty acids. Diogenes (Diet, Obesity and Genes) research is also financed within the scope of the EU Framework Programme. This research is being conducted by 29 European research institutions, and the University of Maastricht is the secretary. The aim is to gain a better understanding of how obesity arises and what role nutrition and heredity play in it. The ultimate aim is to provide a basis for ideas for innovative products and nutritional concepts to help people avoid gaining weight. Participation by industry should enable the concepts to be achieved.

The aforementioned universities and VU University Amsterdam conduct the applied research and it is funded by ZonMw, charitable funds such as the Dutch Heart Foundation and the Dutch Cancer Society (KWF), as well as food manufacturers. Funding from manufacturers is mainly in the form of contractual research. Applied research is research into ways of improving public health through interventions in the nutritional situation. This type of research is divided into:

- research into intermediate end points, such as blood pressure, blood sugar level, and cholesterol. This is usually short-term research;
- research into clinical end points, such as death, disease and quality of life. This is mainly long-term research.

ZonMw, charitable funds and manufacturers mainly fund applied research at intermediate end points. Manufacturers have no direct influence on the research agenda of ZonMw and charitable funds but in their present subsidy policy ZonMw and NWO encourage researchers to cooperate with institutions and companies that develop commercially innovative activities in the health care market. This sets high demands for maintaining research independence. The Ministry of Health, Welfare and Sport has a great deal of influence on ZonMw's agenda because the ministry earmarks funds for particular programmes. Manufacturers determine the research agenda for research they commission universities and research institutions to conduct (contractual research).

Applied research into clinical end points

It is generally difficult to attract funding for applied nutritional research into clinical end points. Manufacturers conduct little research of this kind because demonstrating a causal relationship between a food or ingredient and the health of trial subjects requires long-term trials, which are expensive. There is also little likelihood of ZonMw conducting trials to study the relationship between foods or ingredients and health/disease, not only because the cost usually exceeds the ZonMw budgets but mainly because trials of this kind are at the interface of fundamental research and applied research, which makes them difficult to fit into the programmes. Themes that are of major importance for public health are consequently not taken up. These include research into the relationship between food ingredients and health (lycopene to combat prostate cancer, flavonoids to combat cardiovascular diseases, the role of carbohydrates in the development of diabetes). The market provides no mechanism for recouping the cost of research and development; a company that invested a lot of money in this type of research would jeopardise its own continuity.

For example, tea is highly promoted with references to anti-oxidants. However, a tea manufacturer would not give heart patients tea or tea extracts for several years to study whether they had a heart attack. The risk that it might prove ineffective is too great. However, even if it proved to be effective the producer would still lose the funds invested because tea cannot be patented.

However, applied research into clinical end points is occasionally conducted in the Netherlands, for example when it is possible to attract the interest of various sponsors, as in the case of the large-scale intervention research conducted by the University of Wageningen into the effect of n-3 fatty acids on cardiovascular diseases. This is mainly funded by the Dutch Heart Foundation. The research was also made possible by the National Institute of Health (NIH) in the United States and a margarine manufacturer that contributes by developing, producing and distributing margarine.

Another form of applied research related to nutrition is research into the effects of providing information on a healthy lifestyle. This type of research could also be seen as part of public health research (see section 2.8). Within the scope of its Academic Collaborative Centres for

Public Health programme, ZonMw funds the National Lifestyle Campaigns programme, part of which is concerned with nutrition. The aim of the programme is not only to carry out the campaigns but also to improve their quality and evaluation. The programme includes research into the effects of the information. Industry cannot influence the selection of the parts to be evaluated. The programme is in keeping with the policy priorities of the Ministry of Health, Welfare and Sport.

In April 2007 ZonMw published a programming study commissioned by the Ministry of Agriculture, Nature and Food Quality and the Ministry of Health, Welfare and Sport: *What shall we eat? Challenges for research into nutrition and health in the Netherlands*. It identified nutritional and health research needs. ZonMw is currently developing a long-term programme with joint funding from the Ministry of Health, Welfare and Sport and the Ministry of Agriculture, Nature and Food Quality: 'Healthy nutrition'. A total of four million euros has been provided for the programme's implementation during the period from 2010 to 2013. The research will examine questions such as:

- to what extent do novel foods vis-à-vis traditional foods contribute to healthy dietary habits?
- is there a link between dietary habits and the development of chronic diseases? If there is, what is the relationship?
- what are the determinants of consumer behaviour?

This all focuses specifically on the target groups low Socio-economic status (SES), young people, the chronically ill and elderly people (Jaarplan ZonMw 2009, Programmarapportages, dl II, pages 63-64). Only limited funding is available for this ambitious research programme.

Conclusion

The conclusion is that industry exerts an influence on the agenda for basic nutritional research because it provides a considerable amount of the funding. Contractual research is another way in which industry influences the agenda for applied nutritional research into intermediate end points. Applied nutritional research can be divided into contractual research for industry and research programmes for ZonMw, supported by the Ministry of Health, Welfare and Sport and the Ministry of Agriculture, Nature and Food Quality. Applied nutritional research into intermediate end points still has many 'blank spots'. Almost no intervention research is conducted into the relationship between foods and clinical end points. Research of this kind is hardly ever conducted or funded by the food industry. The high costs and difficulty of fitting it into the programming mean that it also fails to qualify for subsidies from ZonMw or NWO. Themes that are of major importance for public health are consequently not taken up.

2.8 Case study: public health research

The term public health refers to both the health of the public and social activities concerned with protecting or promoting the health of the public. Public health *research* is by definition

concerned with a population or parts of a population. It can be divided into three types: 1. Descriptive research (which delineates trends, for example); 2. Determinant research (determinants of a healthy/unhealthy environment or healthy/unhealthy behaviour); 3. Intervention research (knowledge of effects of interventions, preventive or otherwise). Nutritional research as defined in section 2.7 could also be seen as part of public health research. The same applies to research discussed in section 2.6 into screening methods and do-it-yourself tests.

The broad field of public health research differs from that of drug research and research into diagnostic devices. It was decided to explore this field precisely because of the effect of this contrast. Commercial interests play a role in drug research and research into diagnostic devices; this research is concerned with the manufacture of products on which profits can be made. To do so, companies have to market the products. If certain research is a precondition for this, companies will make a commercial assessment about investing in the research concerned.

Conversely, the field of public health research does not generally involve any commercial interests and products that have to be marketed. Descriptive research and determinant research are not conducted in this field with a view to making products financially lucrative but in connection with public health interests. Behaviour-oriented interventions could possibly be classified as 'products'. Consider for example information campaigns; interventions which teach people with a chronic disease how to improve the way they deal with it; interventions to combat smoking; or movement therapy programmes for overweight people. However, if they exist at all, marketing opportunities for such 'products' are very limited, also because the products are not patentable. Private financiers in the profit sector express little, if any, interest in developing them. Because public health research is concerned with protecting or promoting public interests, knowledge development is mainly dependent on public funding. Most public health research is paid for with public funds. Industrial sponsors therefore have no influence at all on the agenda for public health research. However, the lack of industrial sponsoring in this field is most certainly apparent in knowledge development.

The situation is less clear-cut in some subsectors of public health. The development of vaccines for use throughout the population or screening techniques is more comparable with the development of drugs, as major commercial interests play a role alongside public health interests. This also applies in the case of research into the effects on public health of products for which marketing opportunities are threatened (realistically or otherwise) by health risks, for example the development of mobile telephony. This has led to unrest in the community about the supposed hazardous effects of mobile phone masts on surrounding residents and of mobile telephones on their users. The business sector has a keen interest in the results of public health research such as research into the health risks of mobile telephony. There was consequently a great deal of discussion about the possible contribution of private financiers to the ZonMw Electromagnetic Fields and Health programme. The Dutch government ultimately decided not to join forces with private financiers in the profit sector.

There are also other fields of public health research which involve commercial interests and in which manufacturers might be willing to invest. These include research to ascertain the harm (or absence of harm) to the health of young people caused by drinking *Breezers* or other alcoholic drinks, or the consumption of *fast food*. If public-private partnerships in funding this type of research were feasible, it would in any case be necessary to guarantee the independence of the research owing to the profit sector's major interest in obtaining particular results, namely evidence of the absence of harm to health.

However, the qualification that commercial interests of this kind exist in some subsectors of public health does not undermine the conclusion regarding the majority of public health research. The conclusion is that public health research, which is by definition in the public interest, depends almost entirely on public funding.

Structure and funding of public health research

Public health *research* takes place at various University Medical Centres (UMCs). The research at UMCs usually receives funds from the first flow of funds, although the amounts are relatively modest. Systematic public health funding also concerns funds, possibly labelled, which go straight to institutions outside the university which conduct public health research, namely the National Institute of Public Health and Environmental Protection (RIVM), the Netherlands Organisation for Applied Scientific Research (TNO), Netherlands Institute for Health Services Research (NIVEL), the Netherlands Institute of Mental Health and Addiction (Trimbos Institute) and various Municipal Health Centres (GGDs).

Public health research largely depends on project-based funding by ZonMw. In the nineteen-nineties various small funds of the Ministry of Health, Welfare and Sport and the Prevention Fund were merged into one large fund: ZonMw, the Netherlands Organisation for Health Research and Development. The ZonMw Prevention programme, the Academic Collaborative Centre for Public Health (AW-PG) programme, and the relatively new Youth Health Care programme are important sources of funding for public health research. This always concerns temporary funding. The aim of the AW-PG programme is to obtain more systematic funding from other sources, such as university centres and municipal authorities.

Research in the field of employment and health, which can also be seen as public health research, has a different type of funding. It is not funded by the Ministry of Health, Welfare and Sport and the Ministry for Youth and Families but by the Ministry of Social Affairs and Employment and the large social security implementing bodies, such as the Employee Insurance Agency (UWV) and the former Joint Administration Office (GAK). This is temporary funding but sometimes involves relatively large, long-term research programmes.

Composition of research agenda

Given its central role in funding public health research, government also has a significant say in the composition of the research agenda in this field. Prioritising would be unavoidable even

if public funding for this research was increased. Some subjects will receive more attention than others. The decision on which knowledge gaps will remain and which will be closed is ultimately subject to political consideration. The process of political decision-making is not discussed further here but it is clear that all kinds of particular interests may play a role.

The Advisory Council on Health Research (RGO) advises the government on the composition of the research agenda for public health research. RGO has been closely involved in this research since 2000 and has identified numerous gaps in knowledge on public health, in the field of determinant research, for example. RGO took the view that the largest need for research was in the field of interventions. The things RGO called for included an incentive programme to be set up under the responsibility of ZonMw to tackle the gaps in determinant research and intervention research.

The RGO advisory reports on public health (2000-2003) resulted in a ZonMw programme for Academic Collaborative Centres for Public Health, and in nine collaborative centres. RGO's recommendations for determinant research and intervention research were not really worked out in detail in ZonMw's third Prevention Programme. RGO presented an advisory letter in February 2009 on the content of the fourth Prevention Programme. RGO's advisory letter placed the emphasis on translational prevention research, methodological innovation, screening and systematic evaluation of the prevention programme.

The fourth Prevention Programme started in June 2009. The programme's priorities are:

- Prevention of lifestyle-related disorders by promoting a healthy lifestyle and healthy living environment
- Prevention of psychological disorders that cause a high burden of disease and affect participation in the community and the quality of life
- Early detection through population screening and screening programmes
- Preventive interventions in care.

The fourth Prevention Programme has seven sub-programmes. One such intervention (Gezonde Slagkracht), the ZonMw programme concerned with obesity, alcohol, smoking and drug use, focuses on supporting public health. Adopting an integrated approach, it encourages the further use and distribution by local authorities of projects that have proved to be effective. The aim is also to further develop, i.e. theoretically substantiate and describe, promising local interventions concerned with preventing obesity, alcohol misuse, smoking and/or drug use, and arrange for them to be presented for accreditation by RIVM's Centre for Healthy Life Style. Duration: 2009 to 2014; budget: 10 million euros.

Conclusion

The conclusion is that industrial sponsors have no influence over the research agenda for most public health research: companies rarely fund public health research because there are few, if any, opportunities for making public health 'products' financially lucrative. Research in

this field is very largely paid for by public funds. Government rather than the business sector sets the agenda and priorities for this research. All kinds of particular interests may play a role in government prioritisation but analysis of this decision-making process is beyond the scope of the present advisory report. A relatively large part of public health research takes place in institutions outside universities. Public health *research* largely depends on project-based funding, owing to the limited availability of systematic sources of funding. Gaps in knowledge of public health mainly relate to the determinants of a healthy/unhealthy environment and healthy/unhealthy behaviour, and to interventions.

3 Industrial sponsoring and research

This chapter first summarises the main results of the case studies discussed in the previous chapter (drug research, and research into diagnostic devices, healthy nutrition and public health). We indicate what is known about the influence of industrial sponsoring on the research agenda in the four subsectors of medical knowledge concerned and examine the mechanisms that play a role in this (3.1). We continue with a description of what is known of the influence of industrial sponsoring on knowledge development through research (3.3 and 3.4). The findings are always described in relation to an ethical perspective: what ethical questions arise from the findings (3.2 and 3.5)? Adopting a prescriptive framework as far as possible, the next chapter offers suggestions on how the identified problems might be tackled, whereby the focus is on the influence that the various parties concerned are able to exert.

3.1 How the research agenda is influenced by sponsoring

The first stage of the cycle of knowledge development is that of setting the agenda and priorities for areas in which knowledge has to be developed. We examined this stage in the preceding chapter by means of four case studies.

Results of case studies

The case study on drug research showed that the pharmaceutical industry mainly sets the agenda for research that is required for the registration of a drug. This is understandable from the manufacturer's point of view. However, if knowledge development depended entirely on the agenda that industry sets for research, a great deal of knowledge needed for rational decision-making on patient treatment would be absent. Important gaps in drug knowledge concern:

- The development of drugs for rare disorders (orphan drugs)
- The value of new drugs in daily medical practice
- The efficacy of drugs in specific patient groups, such as those composed of children, elderly people, or patients with more than one disorder
- The long-term effects of drugs
- The side-effects of drugs
- The responsible phasing out of drugs

- The effects of drugs vis-à-vis other interventions (surgical interventions, counselling, movement therapy, dietary changes).

A particularly striking point in the case study concerning diagnostic devices is the limited knowledge of diagnostic validity and clinical benefit of diagnostic instruments, especially in the case of do-it-yourself tests. Manufacturers will only put research into this subject on the agenda if EU regulations make it a precondition for permission to market the products. Knowledge of the diagnostic validity and clinical benefit of products of this kind is a good example of the type of knowledge that doctors or lay persons ought to have to enable them to take rational decisions on the use of the products.

Thirdly, there are the main results of the case study concerning nutritional research. Industry exerts an influence on the agenda for basic nutritional research because it provides a considerable amount of the funding. Contractual research is another way in which industry influences the agenda for applied nutritional research into intermediate end points (blood pressure, blood sugar level, cholesterol, etc.). This research still has many blank spots. Applied nutritional research into clinical end points (morbidity, mortality, quality of life) can best be described as one big 'blank spot', yet this intervention research is of major importance for public health. There is little likelihood of getting the food industry interested in it.

The final case study is on public health. This showed that industry exerts no influence at all on the research agenda for most public health research. Companies do not usually fund public health research, because prospects for making products in this field financially lucrative are generally lacking (although they do indeed exist for some components of public health). Government largely determines the agenda and priorities for research in this field, whereby political considerations and frequent compromises have to be made. There are also large gaps in knowledge of public health, especially regarding the determinants of a healthy/unhealthy environment and healthy/unhealthy behaviour, and regarding interventions.

Analysis

The fields of knowledge studied are subject to all the consequences of what is also known as *crowding out*. This refers to the phenomenon that in fields of knowledge in which product sales and making profit play little, if any, role, development lags behind development in economically valorisable fields of knowledge, even if there is a definite need for the knowledge concerned from the public health point of view. In the case studies we discovered several mechanisms which can play a role in this crowding-out effect. The main ones are:

- Firstly, industry tends not to conduct more research than is required for a new product's registration, as in the case of drugs and diagnostic devices
- Secondly, there are relatively few possibilities for patenting, as is the case with research into the effect of foods on health and in the case of public health research

- Thirdly, the demand for commercial products is sometimes too low in certain domains, such as public health.

3.2 Ethical questions concerning research agenda-setting

We have defined some ethical questions below that arise from the above findings:

- Does the phenomenon we describe as *crowding out* lead to a lack of balance or possibly even a lack of justification in selections and results concerning knowledge development?
- Should industry and other research scientists be permitted to set their own research priorities? Are there limits to freedom of this kind?
- Does government have a responsibility 'to steer'? When? On what grounds? How much funding should government invest in knowledge development that is important from the public health point of view?

These fundamental questions are only raised here and not answered. The questions will require further discussion. Chapter 4 provides suggestions on the direction to take in starting to answer some of the questions.

3.3 How sponsoring influences knowledge development through research

In the development of knowledge, the stage of setting the agenda and priorities is followed by that of developing knowledge through research. A summary is provided below of what is known from international reference literature about the influence of industrial sponsoring during this stage.

Results of reference literature study

The influence of sponsoring on research has been written about extensively over the years and hotly discussed. Chief editors of major medical journals focused attention on the problem.²⁴⁻²⁷ The percentage of clinical trials funded by industry over the past ten to fifteen years has certainly increased sharply.²⁸ Frequently arising aspects of sponsored trials are the following. The research protocol is drawn up in cooperation with industry. Industry or a trial agency contracted by industry often recruits the necessary doctors and possibly also the patients, and collects the data. Industry sometimes performs the data analysis. The manuscript is sometimes written in collaboration with industry. Co-authors often include industry employees and other authors are often consultants to the same industry. In extreme cases they may even hire a *ghostwriter*.²⁹ However, it is often emphasised that authors were always able to examine the research data and concurred with the publication.³⁰

International literature shows that when a company funds research into one of its own products, the results are more favourable for the product concerned than the results of alternatively funded research concerning the same product. In short, research sponsored by industry is significantly more often favourable for the product of the industry concerned. Exam-

ples of cases in which this has been demonstrated include a third-generation oral contraceptive³¹, calcium-channel antagonists³², and statins³³. This also applies to nutritional research into soft drinks and milk³⁴ and of a compound for losing weight (sucrosepolyester)³⁵. Systematic reviews³⁶, meta-analyses^{37,38} and pharmaco-economic studies (cost-effectiveness studies)^{39,40} are subject to the same distortion.

This distortion in favour of the sponsor's product is disturbing, also because it can harm trust in research. If the results of systematic reviews and meta-analyses are also questionable, there is a danger of the basis of guidelines – in fact the entire concept of *evidence-based medicine* – being undermined. This could destroy the basis of decision-making on patient treatment in the field. Moreover, patients who participate in clinical trials should be able to count on the trial being scientifically sound and that it will lead to an honest report in scientific reference literature. It would otherwise be unethical to ask them to participate in such trials.

Analysis

An important question concerns how this distortion in favour of the sponsor's product can be explained. Vandenbroucke and Van der Meer³⁰ provide explanations at three levels, namely a. comparisons using a placebo, b. selective publication, and c. the selection of a favourable comparison.³⁷

COMPARISON WITH A PLACEBO

The new drug is compared with a placebo whereas the comparison ought to be made with a proven efficacious treatment. This was also mentioned in section 2.5. Vandenbroucke and Van der Meer emphasise that in that case an essential principle of a *randomized controlled trial* has not been fulfilled: the uncertainty principle. According to this principle, the odds of each of the compared therapies emerging from the trial as the best must be equal. The real question concerns that about which there is genuine uncertainty. This question is concerned with whether the new drug is more efficacious than existing drugs, rather than whether the new drug is more efficacious than a placebo, and this is indeed likely to be the case, if the new drug comes from a class of efficacious drugs. A placebo is used more often in sponsored research than in unsponsored research and the results for a new drug are consequently more likely to appear favourable.⁴¹

SELECTIVE PUBLICATION

Favourable trial results are published more often than unfavourable trial results.⁴²⁻⁴⁴ There are various reasons for this, one of which is the influence of the sponsor. Researchers play a part in this too, as they are less likely to provide journal editors with a report on research that did not lead to a positive result, on the assumption that it will be rejected anyway. Journals editors (editors and reviewers, as the case may be) influence the selection process; they are mainly interested in publishing articles that have consequences for clinical practice or the way of thinking about a disorder. Sponsors themselves will also put more effort into ensuring publication of a trial report with favourable results; details of such a trial are often published several

times and the authors put forward the most favourable results. Another factor that plays a role is that the publication of sponsored trials is a substantial source of income for journals, as the sponsor is sure to purchase reprints.

CHOOSING A FAVOURABLE COMPARISON

In comparative research, comparisons are chosen which are more likely to increase the odds of the outcome for the experimental drug being favourable. For example, a drug is chosen which is likely, or is known, to be inferior. Or more underhand, the administered dose of the control drug is slightly lower than the standard dose, whereas a slightly higher or variable dose of the experimental drug is administered. When the aim is to demonstrate that the experimental drug has fewer side-effects, the administered dose of the control drug is slightly higher than that of the experimental drug. Research results can also be influenced by selecting subjects/patients or not properly taking into account those who drop out.²⁶ The fact that such methods are indeed used is clear from research in which published data can be compared with registration data.^{42,43} Results become more favourable in relation to an increase in the health of the research population. It was pointed out in section 2.5 that drugs are often tested in a younger research population, with milder comorbidity and fewer severe disorders than the group for which the drug is actually intended. Such factors can lead to bizarre results.³⁰ For example, successive trials of various manufacturers found that drug A was better than drug B, drug B was better than C, and C was in turn better than A, depending on which manufacturer funded the trial concerned.⁴⁵

To what extent do findings like this also apply to medical research in the Netherlands? Is it true, as some parties assume, that such trials in the Netherlands are less susceptible to this type of influence because the trials are subject to the requirements of the Medical Research (Human Subjects) Act and supervision and review by METC and/or CCMO? We cannot answer these questions because no research has been conducted on this subject and opinions of experts and those concerned differ widely. However, medical research in other EU countries and in the United States, where the majority of medical research is conducted, is also subject to supervision and review.

Be this as it may, the fact is that, like doctors anywhere else in the world, when treating patients, doctors in the Netherlands have to base their decisions on evidence obtained from international reference literature. If this is subject to distortion, it interferes with decision-making in the Dutch health care sector too.

3.4 Research for marketing purposes: seeding trials

The stages of disseminating the newly acquired knowledge and its application in the field start once the research has been completed. It is an acknowledged fact that manufacturers exert a great deal of influence in favour of their own product in these stages too.¹ However, these stages are beyond the scope of this advisory report (see section 1.2).

Here we only discuss the phenomenon of seeding trials; these trials are conducted under the pretext of scientific research during phase IV, the phase after a new drug's registration, and are used solely for marketing objectives. Rather than being based on any genuinely interesting question their purposes is to encourage doctors to prescribe a new drug by familiarising them with it. Randomly selected from international reference literature, an example of a seeding trial is the ADVANTAGE trial, in which the drugs rofecoxib and naproxen were compared.⁴⁶

In April 2009, the Dutch Health Care Inspectorate published a report on a study of seeding trials.⁴⁷ It comprised a study of reference literature, interviews and an analysis of documents from the licensees of various drugs. The aim was to discover the mechanism of phase IV research with marketing objectives, so that when requested to participate in them, practitioners would be aware of what was really being asked of them before deciding whether to take part. The mechanism turned out to involve a combination of elements, such as large numbers of practitioners and patients, excessive payments in relation to the work to be done and a lack of clarity about the usefulness and necessity of the trial. Phase IV research that is used for marketing purposes is mainly found in the category phase IV not subject to the requirements of the Medical Research (Human Subjects) Act*, and then mainly for certain drug groups, including *me-too* preparations. According to the inspectorate, the number of patients involved in seeding trials in the Netherlands annually ranges from in the tens to in the thousands.

3.5 Ethical questions concerning knowledge development through research

- What are the ethical implications for the actions of doctors/researchers and their institutions in the light of the discovery in the reference literature of distortion in favour of the sponsor's product? What are the implications of this for science journals and their editorial staff? Are there implications for industrial sponsors/manufacturers?
- Is the distinction between phase III and phase IV research important in decisions of doctors/researchers about whether to cooperate with sponsored research?
- Does the Dutch government have a responsibility to steer? On what grounds? What could the government do?

These questions could also be discussed in greater detail. The next chapter provides suggestions on the direction to take in starting to answer some of the questions.

* Medical Research is defined in section 1, subsection b, of the Medical Research (Human Subjects) Act as research in which activities or ways of behaving are imposed on trial subjects. This is always the case in phase I, II and III research. This is therefore always subject to the requirements of the Medical Research (Human Subjects) Act. However, in phase IV research activities or ways of behaving are not always imposed on trial subjects. For example, no extra activities are imposed on patients when they are already receiving the drug as part of their treatment and the data are collected on the basis of activities which already take place within the scope of their care. In such cases the research is not subject to the requirements of the Medical Research (Human Subjects) Act and it need not be reviewed by METC or CCMO.

4 Guide for the parties concerned

Adopting a prescriptive framework as far as possible, this chapter provides suggestions on how the identified problems might be tackled, whereby we first focus on research agenda-setting (section 4.2) and then on the research (section 4.3). The question always concerns the contribution to possible solutions that can be provided by the various parties involved (doctors/researchers, journals and their editorial staff, industrial sponsors, government). The findings of the preceding chapters are first recapitulated (4.1).

4.1 Summary of the findings

CONCERNING INDUSTRIAL SPONSORING

- Industry sets the research agenda on the basis of its own mission (*drug development*)
- This involves conducting *me-too* trials
- Not all the research conducted by industry is reported in scientific literature
- There is a risk of research being distorted in favour of a manufacturer's own product.

CONCERNING GOVERNMENT

- Without publicly funded drug research, knowledge of drugs will remain limited
- Knowledge development in some subsectors, such as public health, largely depends on public funding
- Government encourages universities to use money from the first flow of funds to attract money from the fourth flow of funds (funding from industry)
- Government encourages public-private partnerships in the field of research (TiPharma and TiFN, for example)
- Government is pulling back and has only limited involvement with the content of research agenda
- Government expenditure on research is relatively small.

4.2 How should research agenda-setting be tackled?

This advisory report identified important gaps in biomedical knowledge and discussed why industrial sponsors will not be filling in these 'blank spots' in the near future. These findings should be cause for the parties concerned (doctors/researchers and their institutions, industry, government) to reflect further (in public) on their role and responsibility in funding and setting

the agenda and priorities for biomedical research. Aspects of the prescriptive framework are always mentioned which they could use for this. This enables the parties concerned to contribute to the social debate on the subject.

By doctors/researchers and their institutions

Section 2.3 described the forces to which clinical research in the Netherlands is exposed and the situations in which there is a likelihood of dubious research. The potential research capacity and the number of available trial subjects/patients in biomedical research are limited. In view of the results of the case studies and the *crowding-out* effect (section 3.1), the concern is that this capacity is not always used to generate the most urgently needed knowledge from the public health point of view.

It was also stressed that in the Netherlands scientific and ethical appraisal of medical research involving human subjects is subject to the regulations of the Medical Research (Human Subjects) Act. The research should be able to meet the scientific and ethical requirements of a recognised Medical Ethics Review Committee (METC) or the Central Committee on Research Involving Human Subjects (CCMO). One of the statutory requirements is that it must be plausible that the research will lead to new medical insights. Research for which this is not plausible should be rejected by an METC.

However, doctors, researchers, research managers and directors of research institutions, care institutions and academic centres cannot shift their responsibility for the composition of the research agenda to an METC. This falls under their own responsibility. Composing a research agenda involves making decisions on the use of the research infrastructure and the burden on the patient population. These decisions have an ethical aspect: the research infrastructure and patient population should be used for research which fulfils a public health or scientific need. The public health interest should weigh heavily in agenda-setting and prioritisation. Placing research projects on the agenda that are less useful from the public health point of view to obtain income for a research group, raises the question of whether the interest served by this is in proportion to the objections and the risk to the trial subject (section 3, subsection c, WMO).

It is extremely important for doctors, researchers, research managers and directors to not only discuss their research agenda with each other, but also their reasons for giving one research project a higher priority than another, so that they continue to be critical of each other and keep each other alert. The Association of Medical Specialists could play a role in this. The review framework of the WMO could be helpful in these discussions.

By industry

Research would be in conflict with the WMO if it could not reasonably be expected to produce new medical knowledge; an example of this would be research into a drug that could at best only be as good as an existing drug, also with regard to side-effects (*me-too* trials). Research

of this kind may well be placed on an industrial agenda but there would be statutory objections to conducting it in the form of a clinical trial in the Netherlands. It goes without saying that companies must abide by the law when conducting research.

It is not a task of the Health Council of the Netherlands and the Centre for Ethics and Health to present companies with a prescriptive framework for composing their research agenda. Scientific and corporate objectives are different; there is nothing wrong with this. However, all parties, including industry, are accountable for the social responsibility. Recommendations in the WHO report on *Priority Medicines*, for example, have not only had an impact on TiPharma's research agenda but also on those of individual pharmaceutical companies. Corporate Social Responsibility offers a prescriptive framework that can help companies critically analyse their own operations (see further <http://www.mvonderland.nl/>).

Within the scope of the recommendation below to increase funding for research, manufacturers could voluntarily contribute to one or more public funds, without setting conditions on how the funds must be spent. Such a gesture could be made by the pharmaceutical industry in particular, also in aid of restoring its image, which has become rather tarnished over the past decade. Manufacturers of medical equipment could contribute, as could other companies that receive their income or part of it from health care, such as the ICT sector.

By government

According to section 22, subsection 1, of the Dutch Constitution, it is the government's duty to take measures to promote public health. Part of this duty is to foster the development of medical knowledge because it is essential for public health. Government has the freedom to decide how ambitiously it fulfils this subtask. Government has been retreating over the past twenty years and has mainly fulfilled this subtask by providing funds for research and encouraging public-private partnerships. However, government funding for research has remained below the norm agreed within the EU for research. Moreover, public-private partnerships will not focus on knowledge that cannot be economically valorised, yet there is a major need for this knowledge in the field.

Government could fulfil its constitutional task of knowledge development with a higher level of ambition. It could do this by increasing research funding and more actively steering the way the agenda and priorities for subjects are set in order to compensate for the crowding-out effect (see section 3.2) and unbalanced growth in knowledge development. By becoming more actively involved in research agenda-setting, government could promote the development of knowledge which is hardly, if at all, valorisable and could encourage investigator-driven research. It could adopt various approaches to this.

Firstly, government could endeavour to create a better balance between the various flows of funding. Since the nineteen-eighties, central government has urged universities to use money from the first flow of funds to attract money from the fourth flow of funds (contractual

research), a policy which has certainly borne fruit. However, tension exists between this policy and compensating for 'market failure' and crowding out, it has traditionally been the task of academia to develop knowledge that is not economically valorisable. Government policy could impede this traditional academic task. This aspect would deserve to be considered when evaluating policy.

Secondly, government has the option of actively encouraging the development of biomedical knowledge to fill in the 'blank spots'. We identified the blank spots in chapter 2 by exploring four subsectors of medical knowledge, namely drugs, diagnostics, healthy nutrition and public health. Deploying more research funds through the second flow of funds (earmarking) would enable government to actively promote knowledge development in particular fields.

In chapter 3 we identified the mechanisms that play a role in the emergence of blank spots in the four subsectors. However, these mechanisms are not equally relevant for all four subsectors. Each subsector has its own dynamics: a given field is mainly affected by one mechanism while a different mechanism affects another field. Therefore, solutions for the agenda-setting problem of each of the subsectors should not always be sought in the same direction. The directions in which solutions should be sought may be different, depending on the dynamics of the subsector concerned. It may sometimes also be advisable to have different incentive measures alongside each other.

One possibility could be to incorporate more incentives in existing regulations, at the EU level or otherwise, to encourage the business sector to conduct particular research. Various options could be considered for this:

- Tightening registration rules. A precondition for registering a drug could for instance be the manufacturer's provision of funds for (independent!) phase IV research into that drug, to enable its long-term effects to be studied, for example. Another example is using stricter registration rules to compel independent research into the responsible phasing out of drugs
- A tax benefit for companies that conduct certain research. This option was chosen to encourage research into orphan drugs
- Increased patent protection in return for certain research. This method is used to encourage drug research involving children. The patent on a drug can be extended by six months if the results of a trial involving children are submitted to the registration authority at the time of the drug's registration
- Clarification or tightening of the 'essential requirements' of European directives (the IVD Directive, for example) so that a diagnostic device may only be marketed if proof of its diagnostic validity and clinical benefit can be submitted. An intermediate step towards such a tightening of the requirements could be the temporary approval of a diagnostic device, subject to obliging the manufacturer to deliver the aforementioned proof within a given period

- Facilitating legislation and regulations at the EU level and national level. Examples include the Regulation on medicinal products for use in the Paediatric population and the Regulation on Orphan Medicinal Products.

European law restricts the possibilities for incorporating incentives for the business sector in national regulations. However, even if such possibilities were available, it would still not be advisable to have stricter rules than other EU countries, in view of the repercussions for research this could have on the market. This is because companies will tend to move their research to countries where the rules are less strict.

Thirdly, government can jointly determine the development of the research agenda for Public-Private Partnerships (PPPs) such as TiFN and TiPharma. The underlying idea of Public-Private Partnerships was that partnerships of this kind would enable government to influence the research agenda. However, the extent of government influence in recent years is unclear: no research has been conducted into how PPP agendas and priorities are established (see *Background study*). The business sector appears to have more influence than the government on the research agenda of TiPharma and TiFN. Be this as it may, becoming more actively involved with the research agenda of PPPs would enable government to arrange for the development of valorisable knowledge that is of major importance for public health to be placed high on the research agenda of PPPs of this kind.

The PPP model is unsuitable for generating knowledge of interventions which cannot be used to earn money, which is the case with many public health interventions. Developing this type of knowledge will continue to depend on public and charitable funds. The fourth approach government could take to compensate for the crowding-out effect would therefore be to increase public funds for research, in a situation in which the Netherlands continues to fall short of the norm for R&D investments set by the EU. Obliging the pharmaceutical industry, for example, to donate a percentage of its turnover to one or more public funds would provide a fundamental increase for research that is relevant to public health, such as non-commercial drug research. Italy opted to adopt this type of obligation (five percent of the pharmaceutical industry's marketing budget, which represents an annual sum of around 40 million euros).⁴⁸ The idea is that the research agenda of these funds can be devoted entirely to the public health need, without any commercial influence. However, the authors of the *Background study* doubt the possibility of preventing commercial influences on the research agendas of these funds; in their view the commercial sector and public sector are too intertwined.

In the past there was a lack of support for this option in the Netherlands but this could change. A sensitive issue continues to be that this approach could compel the business sector to contribute funds for generating knowledge with which it would ultimately have to compete (for example the development of an efficacious movement therapy for obesity, which could compete with a pill to treat obesity). This option has the limitation that the intended financial obliga-

tion should preferably be imposed at the international level, otherwise there would be a considerable risk of manufacturers moving to countries that had no such obligation.

The following possibility is another way of achieving a fundamental increase in public funds for research. The pharmaceutical industry lets the community pay towards the costs of R&D for its products; these costs are included in drug prices. By way of analogy with this, a small fixed percentage of the annual turnover of health insurance companies could conceivably be earmarked for research which should be a priority from the public health point of view but which cannot be funded by the private sector or available public funds. This could be used for public health research, but also for quality-of-care research or fundamental research. This would probably result in a slight increase in the insurance premium contributions paid by everyone. However, the intention is for research of this kind to ultimately lead to more clinical utility and efficiency in health care and in health benefits, which could result in a decrease in prices and premiums.

Funds obtained in this way could be transferred to public funds. These funds could enable the money that became available to be divided between biomedical research that meets a public health need, such as non-commercial drug research or public health research. The structure of decision-making on how these funds ought to be spent should include assurances that independent experts will be involved, as is the case with funding through the public research funds. An advantage of such a flow of funding is that it would be constant, thereby making R&D funds less vulnerable to spending cuts than funding per project or programme.

Finally, mention should be made of the recent initiative by the US government to provide a major financial incentive for comparative effectiveness research. The aim is to learn more about the efficacy and cost-effectiveness of various treatments for the same disease. It is intended to make health care decision-making more rational and eventually to save money by discouraging less effective treatments.

4.3 How can distortions in sponsored research be combated?

International literature shows that distortion in the results of industrially sponsored research is a real problem. The distortion relates to the fact that when a company funds research into one of its own products, the results are more favourable for the product concerned than the results of alternatively funded research concerning the same product. Section 3.3 discussed the mechanisms which can lead to the distortion and undermine trust in research.

The position adopted here is not that, in view of the distortion, it would be better to prohibit all industrial sponsoring of research. It would be more advisable to try to solve the problem by ensuring that a counterweight is included in all research to prevent this type of distortion from occurring.¹ It is important to bear in mind the international character of the problem. The

approach to it requires a joint effort at the international level by many countries. The Netherlands can only play a limited role in solving the problem.

The main explanations for the type of distortion discussed were a. comparisons using a placebo, b. selective publication, and c. the selection of a favourable comparison. This immediately provides us with the main starting points for tackling the problem: if an accepted alternative treatment is available, placebo-controlled trials should be further reduced; research results that are disappointing for the sponsor should also be published; the optimum dose must be administered of the drug with which the comparison is being made. In short, the quality of trials should be improved.

An examination follows of the contribution that the various parties concerned could make, and to a considerable extent do make, to solving the problem. Many of the steps towards achieving this have been started in recent years. The parties concerned are: 1. researchers and their institutions, 2. journals and their editorial staff, 3. industry, and 4. government.

By researchers and their institutions

The existing prescriptive frameworks available to researchers are the principles of Good Clinical Practice (GCP), research codes of institutions/hospitals and the KNAW's Declaration of Scientific Independence.⁴⁹ Researchers who conduct contractual research should in any case always ask themselves whether the role of the financier is in keeping with the GCP principles. The Association of Medical Specialists could develop a research code for general hospitals. Scientific associations could draft a code of ethics for biomedical research. Researchers would then be able to publicly undertake to abide by the code, or take an oath or pledge to abide by it in their work. Study programmes of trainee researchers should focus more on the ethics of conducting research (*research ethics*).

The independence of the researcher(s) may be a particularly effective way of compensating for research results that are distorted in favour of sponsors. The compensatory effect increases in proportion to the researcher's independence. Doctors/researchers should adopt a more assertive and aloof and thereby more independent attitude towards industrial sponsors. Reducing conflicts of interest between the sponsor and the researcher reduces the need for the researcher to be 'agreeable' to the sponsor, which reduces the likelihood of bias in research results. Vandenbroucke and Van der Meer cite as an example of an existing construction with a greater distance from industry, the Clinical Trial Service Unit, in Oxford, the UK, where not only the research initiative and design are in the hands of researchers but also all data collection, processing and interpretation, and only the researchers themselves write the publication.³⁰

Researchers can refuse to conduct unnecessary placebo-controlled trials by invoking the Declaration of Helsinki. Research managers can invoke the same declaration to exclude this type of research from their research agenda. Administering the optimal dose of the drug with

which the experimental drug is being compared might seem to be an obvious requirement from the scientific point of view but apparently it is not. The researcher is responsible for research design, data collection and data analysis. This requires the researcher's active involvement. The assignment of responsibilities should be agreed with the sponsor before research commences. These agreements must be ethically acceptable. It is extremely important for researchers/clinicians to take the same line in this, as sponsors will otherwise easily find replacement researchers/clinicians with more flexible standards.

It is not sufficient for people to state that they have abided by the GCP principles; the important issue is verification that the research has actually been conducted in accordance with the GCP principles. The credibility of the results must be verified by monitoring while the research is being conducted. It is precisely this verification which is still inadequate in practice: the quality assurance of research and research institutions needs to be improved. According to the GCP guidelines, research publications should describe how, and on the basis of which assumptions, the results were obtained, and which predetermined statistical methods and statistical supporting information were used. This not only applies to the actual research report but also to journal articles based on the report. Articles must also be GCP-proof.

The possibility of sponsors preventing or delaying publication of research results that they find disagreeable must be prevented. Researchers must ensure that their freedom to publish is guaranteed in the research contract. They should not sign contracts containing stipulations that the sponsor may delay or prevent publications of research results for a long time. They can also stipulate in the contract with the sponsor that any data files relating to the research that are generated will be available in the public domain for secondary analysis.⁵⁰ It is important to have widely available standard contracts, so that researchers are not constantly having to reinvent the wheel in their negotiations with sponsors. An industry-university model contract is being drafted which will safeguard freedom to publish. The second edition of the AMC's Research Code has been published.⁵ In 2005 KNAW drafted a Declaration of Scientific Independence to which researchers and clients can commit themselves.⁴⁹ The Declaration states that the scientist is always free to publish the findings of the research within a reasonable period (two months, with six months generally being the maximum). Since November 2008, METC reviews of research must also assess the content of the research contract, which includes assessing agreements on the publication of results.⁵¹ METCs can counter unnecessary research by stipulating in their review that a clinical trial will only be permitted on condition that its necessity is apparent from a meta-analysis which also includes unpublished trials.

Researchers need to be especially alert in phase IV research (the phase after a drug's registration), as this is the phase in which the sponsor's marketing objectives may play a role. Moreover, not all phase IV research is covered by the WMO (see footnote in section 3.4). Doctors and researchers could develop their own professional standards for research not covered by the WMO.⁴⁷ The aim of this is that, armed with such standards, doctors would be in a better position to assess whether they were being asked to participate in a *seeding trial*. They should

be aware that seeding trials produce no new knowledge and cannot therefore be scientifically justified.

Researchers should in general be open and honest about financial links and conflicts of interest. However, transparency alone is not enough and is certainly not a panacea. Transparency can also have the opposite effect in that openness about conflicts of interest can sometimes intensify the conflicts.⁵² The parties who are open then appear to be more biased, rather than less. Those on the receiving end of openness are also not always aware of how to deal with it properly.⁵² It is therefore more advisable to avoid conflicts of interest altogether. This means, for example, that doctors/researchers receive no personal remuneration or fee and accept no financial support, such as opportunities to attend congresses and payment of the associated costs. It also enhances their credibility, if they are not shareholders in the company sponsoring them. The *Institute of Medicine* (IOM) recommends research institutions to establish a policy that individuals generally may not conduct research with human participants if they have a significant financial interest in an existing or potential product or a company that could be affected by the outcome of the research.⁵³

By journals and their editorial staff

Editorial staff of journals could help promote transparency by requiring researchers submitting a manuscript to complete a declaration of interests statement to be published with the article. The major medical journals have made this their policy.⁵⁴

Editorial staff are helpful in promoting the quality of research by drafting criteria for proper research and proper research reporting (see for example *Consolidated Standards for Reporting Trials* (CONSORT guidelines) of *Standards for the Reporting of Diagnostic Accuracy Studies* (STARD guidelines), by, where necessary, bringing the requirements for manuscript acceptance up to date and tightening them and actually applying the criteria and requirements in editorial decision-making. In the case of placebo-controlled trials, editorial staff must always request written arguments. This helps ensure that the beneficial effects of new drugs are not overstated. They ensure that all the data, including negative data, are published. To combat superfluous research, they make publication of a report on a clinical trial subject to the condition that the necessity of the trial is apparent from a meta-analysis which included not only published but also unpublished trials.

The *International Committee of Medical Journal Editors* (ICMJE), in which many influential medical journals are represented, decided that from 2005 articles would only be published on research that had been reported in a recognised public trial register.⁵⁵ The details of any sponsors must also be reported in the public trial register. Most journals have now made this part of their editorial policy. The aim of this is to combat selective publication and also the withholding of research results that are disagreeable to the sponsor*.

Deciding to make publication of research articles subject to providing the editors with the research design or protocol is taking this even a step further. Editors could decide to place the protocols on a website, to make them available to everyone.⁵⁶ The journal JAMA requires the data of studies sponsored by industry to be analysed by statisticians 'at an academic center' and not just by statisticians of the company that funded the research. Not everyone agrees with this requirement.⁵⁷

Some parties think that all these measures together will still not provide an adequate remedy. A former editor of the *British Medical Journal* has therefore made a radical proposal, namely, stop publishing trials in journals.²⁶ Protocols and results of trials could be made public on regulated websites. Journals would then have the task of critically discussing trials. This is an attractive suggestion but is it feasible? Journals generate a substantial part of their income by publishing sponsored trials, as the sponsor is certain to purchase reprints. Moreover, trials generally attract a large number of readers.

By industry

Industrial sponsors could play a big part in reducing the distortion of research results in favour of their own products. A hopeful sign is that Nefarma, the Dutch Association of the Research-based Pharmaceutical Industry, has sided with the proposed publication of research data from the CCMO register (see below *By government*). Some companies have undertaken to post on their own website, within a specified period, the results of all their research, both positive and negative. US law obliges companies to report their clinical trials to the public register established by the *National Institutes of Health* (NIH) www.ClinicalTrials.gov.

Sponsors who leave as much as possible of research planning and monitoring to researchers show that they understand the problem and are taking responsibility for dealing with it. The less involved the sponsor is in designing and conducting research, the more reliable and authoritative the results will be. In due course, the sponsor can reap the benefits of this too. A question manufacturers should ask themselves is whether they should be involved with RCTs (phase 3 research) or whether it might be better to leave them entirely to independent doctors/researchers to conduct.⁵⁸

Sponsors can commit themselves to the KNAW's Declaration of Scientific Independence.⁴⁹ According to the declaration, the sponsor is never entitled to prevent the publication of research results, and at most may only delay publication by a period of not more than six months (although when issues of intellectual property are involved a period of twelve months is acceptable).

* Vandenbroucke and Van der Meer doubt that reporting in a recognised trial register will be sufficient to achieve the intended effect.³⁰ They believe that an obligation to publish should be introduced, in addition to the obligation to register.

The Medicines Advertising Code Foundation (CGR) is a self-regulating body of the pharmaceutical industry. The Dutch Health Care Inspectorate (IGZ) has proposed that CGR should take responsibility for reducing seeding trials, by, for example, arranging a compulsory preventive review prior to phase IV research, especially that which is not subject to the Medical Research (Human Subjects) Act.⁴⁷ Consultations are underway between the pharmaceutical industry, IGZ and KNMG about setting up a separate review body for this type of research. Industrial sponsors could draw up their own guidelines for good sponsoring practice within the scope of self-regulation, somewhat analogous to the guidelines for *good clinical practice*.⁵⁹

By government

Since the Medical Research (Human Subjects) Act entered into force in 1999, it has been compulsory in the Netherlands to report medical research involving human subjects to CCMO. CCMO's public trial register has been operational since the end of 2008. The application for the register's accreditation by the WHO has been submitted. Publication of the research data contained in this register was originally still on a voluntary basis but in the autumn of 2009 it will become standard practice to place key data from a research protocol in the public CCMO register. The register is prospective and now complies with the list of twenty items drawn up by the WHO which have been adopted by the *International Committee of Medical Journal Editors* (ICMJE). Anyone will be able to consult the register. If accreditation is obtained from the WHO, publication by means of this register will also be recognised by the editors of biomedical journals.

All parties now agree that public *trial* registers are essential for combating selective publication. Is it necessary to include entire research protocols in a register of this kind? Only the key data of protocols will be filed in the CCMO register. Obliging research protocols to be registered and publishing the registered data enables a government to prevent research results from being concealed or details being presented as research results when they are not.⁶⁰ Sir Iain Chalmers, one of the founders of the *Cochrane Collaboration*, is in favour of making research protocols public.⁶¹

The CCMO register does not yet contain any research results. It is the intention to include them in the future. The United States is a step ahead of the European Union with the obligation to report the results of clinical trials. Under *FDA Amendment Act 801*, from September 2008 companies will be obliged by law to place certain research results in the public domain.⁶² And from January 2009 the same will apply to certain data concerning safety.*

The question arises of whether it might not be better for governments to simply prohibit placebo-controlled drug research, unless there is still no effective treatment available for comparison. However, less radical but equally effective methods are conceivable for reducing the use

* This development comes with a warning from the united editors of the *PLoS* medical journals, which are accessible free of charge on the internet: how reliable will results placed in the public domain be, now that their quality is not monitored by peer review? Is there a danger that results will be misused for advertising? Public registers make it all the more necessary to have researchers who are not dependent on the pharmaceutical industry for their income.⁶³

of placebo-controlled trials. Consider for example the possibility of METCs supervising the research more closely or of tightening the registration requirements for new drugs. For example, the new drug could be required to be more effective than the main competitive drugs. Requirements could only be made more stringent in this way at the EU level.

A statutory measure with another purpose and implementable at the national level would be to restrict some points of the industry-university contractual freedom. A statutory restriction like this could for example be used to combat excessive payments for each patient to be included. However, such a measure would only be advisable if the recently tightened METC supervision displayed demonstrable shortcomings. (For details on tightening supervision, see section 4.3 under the heading *By researchers and their institutions*).

In its report on seeding trials the inspectorate recommended that legislation or policy should include general rules on phase IV research that is not subject to the Medical Research (Human Subjects) Act. This recommendation is underscored here. Abuses are made of phase IV research, although the extent of the abuse is unclear.

Government could also help tackle the identified problem indirectly. It could do this by for example promoting the understanding that the independence of science needs to be strengthened, by for example focusing attention on the individual researcher's scientific integrity in education and research.^{5,49,64,65} The ethics of research (*research ethics*) could be given a much more prominent place in the education of trainee doctors/researchers. Government could work to improve the infrastructure for research, to make knowledge development generally less dependent on industrial sponsoring.

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Annex 1

Members of the Standing Committee on Health Ethics and Health Law

- Prof. J.A. Knottnerus, President of the Health Council of the Netherlands, The Hague, *chairman*
- Prof. J.K.M. Gevers, Professor of health law, Academic Medical Centre, University of Amsterdam, *Vice-chairman*
- Prof. J.C.J. Dute, Professor of health law, University of Amsterdam
- Prof. R.P.T.M. Grol, Professor of quality promotion and control in general practice, St Radboud University Medical Centre, Nijmegen
- Prof. G.R.J. de Groot, Professor of social health care insurance law, VU University, Amsterdam
- R.M. den Hartog-van Ter Tholen, Ministry of Health, Welfare and Sport, The Hague, *observer*
- Prof. G.A. den Hartogh, Professor of ethics, University of Amsterdam
- Prof. A.C. Hendriks, Professor of health law, Leiden University/health lawyer, Equal Treatment Commission, Utrecht
- Prof. H. Jochemsen, general manager of Prisma, Houten/endowed Professor of reformational philosophy, Wageningen University
- Dr. W.L.M. Kramer, paediatric surgeon/paediatric traumatologist, Wilhelmina Children's Hospital, University Medical Centre, Utrecht
- Prof. F.E. van Leeuwen, Professor of epidemiology, Netherlands Cancer Institute, Amsterdam
- Prof. J. Legemaate, Professor of health law, VU University, Amsterdam/health lawyer, KNMG, Utrecht
- Dr. G.C.M.L. Page-Christiaens, gynaecologist, University Medical Centre Utrecht
- Prof. MA Verkerk, Professor of medical ethics, University Medical Centre Groningen
- Prof. M. de Visser, Vice-president of the Health Council of the Netherlands, The Hague
- Prof. G.M.W.R. de Wert, Professor of biomedical ethics, Maastricht University
- A. Wijbenga, executive director of the Health Council of the Netherlands, The Hague, *advisor*
- Prof. D.L. Willems, Professor of medical ethics, Academic Medical Centre, University of Amsterdam

- Dr. C.J. van de Klippe, Health Council of the Netherlands, The Hague, *secretary*
- Dr. H.W.J.M. Wijsbek, Health Council of the Netherlands, The Hague, *secretary*

Dr. C.J. van de Klippe acted as author/secretary for this advisory report.

Interviewed experts

- Dr. D. Bijl, chief editor of Geneesmiddelenbulletin
- Prof. H.R. Büller, Professor of internal medicine, head of Vascular Medicine department, Amsterdam University Medical Centre
- Prof. A. Cohen, Director Centre for Human Drug Research
- Dr. M.J.H. Kenter, General Secretary of CCMO
- Prof. J. Lubsen, emeritus Professor of the theory of clinical conduct, Erasmus University, Rotterdam, scientific researcher with considerable experience in cooperating with industry
- Dr. R.W. van Olden, medical director of GlaxoSmithKline
- Prof. F.R. Rosendaal, Professor of clinical epidemiology haemostasis and thrombosis, University of Leiden
- Dr. C. Smit, patient representative
- Prof. J.P. Vandenbroucke, Professor of clinical epidemiology, University of Leiden

Annex 2

Abbreviations

<i>ACOG</i>	American College of Obstetricians and Gynaecologists
<i>AMC</i>	Amsterdam University Medical Centre
<i>AW-PG</i>	Academische Werkplaatsen Publieke Gezondheid (Academic Collaborative Centre for Public Health)
<i>BMM</i>	BioMedical Materials program
<i>GNP</i>	Gross national product
<i>CBG</i>	College ter Beoordeling van Geneesmiddelen (Medicines Evaluation Board)
<i>CCMO</i>	Centrale Commissie Mensgebonden Onderzoek (Central Committee on Research Involving Human Subjects)
<i>CEG</i>	Centrum voor Ethiek en Gezondheid (Centre for Ethics and Health)
<i>CFH</i>	Commissie Farmaceutische Hulpverlening (Committee for Pharmaceutical Help)
<i>CGR</i>	Stichting Code GeneesmiddelenReclame (Medicines Advertising Code Foundation)
<i>CONSORT</i>	Consolidated Standards for Reporting Trials
<i>COPD</i>	Chronic Obstructive Pulmonary Disease
<i>CPMP</i>	Committee for proprietary medicinal products
<i>CTMM</i>	Centre for Translational Molecular Medicine
<i>CVZ</i>	College voor Zorgverzekeringen (Health Care Insurance Board)
<i>EFSA</i>	European Food Safety Authority
<i>EMA</i>	European Medicines Agency
<i>EMRC</i>	European Medical Research Council
<i>ESF</i>	European Science Foundation
<i>EU</i>	European Union
<i>EWP</i>	Efficacy Working Party
<i>EZ</i>	Ministerie van Economische Zaken (Ministry of Economic Affairs)
<i>FDA</i>	U.S. Food and Drug Administration
<i>FES</i>	Fonds Economische Structuurversterking (Economic Structure Enhancing Fund)
<i>GAK</i>	Gemeentelijk Administratie Kantoor (Municipal Administration Office/Joint Administration Office)
<i>GCP</i>	Good Clinical Practice
<i>GGD</i>	Gemeentelijke GezondheidsDienst (Municipal Health Service)
<i>GPD</i>	Gross Domestic Product
<i>GR</i>	Gezondheidsraad (Health Council of the Netherlands)
<i>GSM</i>	Global System for Mobile communications
<i>HPV</i>	Human Papillomavirus
<i>ICH</i>	International Conference on Harmonization
<i>ICMJE</i>	International Committee of Medical Journal Editors
<i>ICT</i>	Information and Communication Technology
<i>IGZ</i>	Inspectie voor de Gezondheidszorg (Health Care Inspectorate)
<i>IOM</i>	Institute of Medicine
<i>IVD</i>	In Vitro Diagnostic Medical Devices
<i>JAMA</i>	The Journal of the American Medical Association
<i>KNAW</i>	Koninklijke Nederlandse Academie van Wetenschappen (Royal Netherlands Academy for Arts and Sciences)
<i>KNMG</i>	Koninklijke Nederlandse Maatschappij tot bevordering der Geneeskunst (Royal Dutch Medical Association)
<i>KWF</i>	Koningin Wilhelmina Fonds voor de Kankerbestrijding (Dutch Cancer Society)

<i>ACOG</i>	American College of Obstetricians and Gynaecologists
<i>AMC</i>	Amsterdam University Medical Centre
<i>LNV</i>	Ministerie van Landbouw, Natuur en Voedselkwaliteit (Ministry of Agriculture, Nature and Food Quality)
<i>LOWI</i>	Landelijk Orgaan voor Wetenschappelijke Integriteit (National Committee for Scientific Integrity)
<i>MCRN</i>	Medicines for Children Research Network
<i>METC</i>	Medisch Ethische ToetsingsCommissie (Medical Ethics Review Committee)
<i>CSR</i>	Corporate Social Responsibility
<i>NFU</i>	Nederlandse Federatie van Universitaire Medische Centra (Netherlands Federation of University Medical Centres)
<i>NIH</i>	National Institutes of Health
<i>NIVEL</i>	Nederlands instituut voor onderzoek van de gezondheidszorg (Netherlands Institute for Health Services Research)
<i>NIZO</i>	Nederlands Instituut voor Zuivelonderzoek (NIZO Food Research)
<i>NWO</i>	Nederlandse organisatie voor Wetenschappelijk Onderzoek (Netherlands Organisation for Scientific Research)
<i>OCW</i>	Ministerie van Onderwijs, Cultuur en Wetenschappen (Ministry of Education, Culture and Science)
<i>PMS</i>	Post Marketing Surveillance
<i>PPP</i>	Public-Private Partnership
<i>R&D</i>	Research & Development
<i>RCT</i>	Randomized Controlled Trial
<i>RGO</i>	Raad voor Gezondheidsonderzoek (Advisory Council on Health Research)
<i>RIVM</i>	Rijksinstituut voor Volksgezondheid en Milieu (National Institute of Public Health and Environmental Protection)
<i>RVZ</i>	Raad voor de Volksgezondheid en Zorg (Council for Public Health and Health Care)
<i>SES</i>	Socio-Economic Status
<i>SoZaWe</i>	Ministerie van Sociale Zaken en Werkgelegenheid (Ministry of Social Affairs and Employment)
<i>SSRI</i>	Selective Serotonin Reuptake Inhibitor
<i>STARD</i>	Standards for the Reporting of Diagnostic Accuracy Studies
<i>TiFN</i>	Top institute Food and Nutrition
<i>Ti-GO</i>	Topinstituut Gezond Ouder worden (Top Institute Grow Old healthily)
<i>TiPharma</i>	Top institute Pharma
<i>TU</i>	University of Technology
<i>UK</i>	United Kingdom
<i>UMC</i>	University Medical Centre
<i>UWV</i>	Uitvoeringsinstituut WerknemersVerzekeringen (Employee Insurance Agency)
<i>VU</i>	Vrije Universiteit (VU University Amsterdam)
<i>VWS</i>	Ministerie van Volksgezondheid, Welzijn en Sport (Ministry of Health, Welfare and Sport)
<i>WHO</i>	World Health Organization
<i>WMA</i>	World Medical Association
<i>WMO</i>	Wet Medisch-wetenschappelijk Onderzoek (Medical Research Involving Human Subjects Act)
<i>ZonMw</i>	Nederlandse organisatie voor gezondheidsonderzoek en zorginnovatie (Netherlands organisation for health research and development)

Annex 3

CEG publications

Monitoring reports

MONITORING REPORTS ETHICS AND HEALTH

2008:

Health Council of the Netherlands

- Care for the unborn child

Council for Public Health and Health Care

- Farewell to non-commitment. Decision systems for organ donation from an ethical viewpoint

2007:

Health Council of the Netherlands

- Should blood donors be tested for Variant Creutzfeldt-Jakob disease?

Council for Public Health and Health Care

- Appropriate evidence. Ethical questions concerning the use of *Evidence* in health care policy
- Financial incentives for organ donation

2005:

Health Council of the Netherlands

- Embryonic stem cells without moral pain?
- Ethical aspects of cost-utility analysis
- Now with extra bacteria! Food products with health claims

Health Council of the Netherlands/Council for Public Health and Health Care

- Tracking down threats to health: screening in GP practice (RVZ)

Council for Public Health and Health Care

- Health care professional and police informant?
- Ethics in health-care institutions and in the education of care professionals

2004:

Health Council of the Netherlands

- Terminal sedation
- Advanced homecare technology: moral questions concerning an ethical ideal

Council for Public Health and Health Care

- Intermezzo
- Advanced homecare technology: moral questions concerning a new healthcare practice

These publications can be downloaded from www.ceg.nl, www.rvz.net or www.gr.nl.