Chapter 5

Health services research at work in Case I

The first case of health services research at work for national health policy concerned the genetic screening programme for familial hypercholesterolaemia (FH) in the Netherlands implemented by the Foundation for the Identification of Persons with Familial Hypercholesterolaemia (StOEH). The initiative for an evaluation was developed by the StOEH together with health services researchers and focused on the costs and effects of the screening programme. The Ministry of Health, Welfare, and Sport (MoH) used the results in the decision-making process regarding the implementation of the screening as a national programme. One of the initial content questions regarded the cost effectiveness of the screening programme. We developed a combination of four content-, context- and process-focused research questions, in addition to the initial research questions formulated in the research proposal:

1) What is the prevalence of a mutation among screened persons with hypercholesterolaemia and the prevalence of hypercholesterolaemia among persons with an LDL receptor gene mutation (FH+)? (presented in Chapter 2 [1])
2) What proportion of patients with FH were identified with hypercholesterolaemia in general practice prior to genetic screening? (presented in Chapter 3)
3) What is the potential of the current methodology of pedigree analysis and follow-up: How many family members can be reached by the programme and how many have already been reached? [2] and
4) Do screened persons (and persons with a positive screening result) face consequences when applying for insurance because of their participation in the screening programme? [3]

In this case, we presented the results of the first and second additional research question in Chapters 2 and 3 respectively. Furthermore, in Chapter 4 we presented the results of the cost-effectiveness study of the programme [4].

The research group consisted of epidemiologists, public health specialists, medical doctors, a health scientist and a psychologist. The work of the research group was supervised by a scientific committee consisting of senior academic researchers [5]. During the evaluation, in terms of frequency of interaction, our most important counterparts were the staff and initiators of the organization that implemented the genetic screening programme, the StOEH [6]. Besides being a counterpart, the StOEH was also a subject of the evaluation, as our evaluation included its approach, programme costs and results. The evaluation study was contracted by the Netherlands Organisation for Health Research and Development (ZonMw).

Inclusion of additional research questions

We used different strategies to pursue all four additional research questions formulated in this evaluation study. It was possible to answer the first additional question – What is the prevalence of hypercholesterolaemia among the screened persons? (Chapter 2) – within the financial boundaries of the initial research proposal. We perceived this study as a necessary content-related intermediate analysis. We received the full cooperation of the StOEH

in linking the results from DNA analysis to the results from cholesterol measurements. No additional data or staff were needed other than those already available.

The second question – What proportion of patients with FH were identified with hypercholesterolaemia in general practice prior to screening? (Chapter 3) – could be addressed through student involvement. A medical student carried out the data collection as part of his obligatory research internship. In addition, the StOEH facilitated in contacting screened persons who were identified as FH+. The StOEH asked these persons for permission to review their medical records in the general practitioner's (GP) practice regarding FH-related matters, such as cholesterol measurements and hypercholesterolaemia treatment. Once permission was obtained, the StOEH had no further involvement in this study. Supervising the student's data analysis and reporting of the study results was done within the framework of the initial proposal and as part of the academic training of the medical student. No additional funds or other resources were used.

We developed a third additional question regarding the analysis of the pedigree and the completeness of the family tree drawn up by the StOEH (not shown in this thesis). A graduate student in medical informatics designed a model for analysing the FH+ population that could theoretically be identified with the chosen approach. Supervision was provided by researchers in the evaluation study as well as by an assistant professor in medical informatics as part of the academic training of the student.

The fourth additional research question – Do screened persons and persons with a positive screening result face consequences when applying for insurance because of their participation in the screening programme? [3] – could also be addressed by involving a medical or other student, much like the second and third additional questions. The StOEH facilitated the informed consent and the mailing of questionnaires. Supervision was provided by one of the senior researchers in the evaluation study. No additional funds were needed.

Interactions with policymakers and other actors

Our experiences with policymakers and other actors in achieving these additional research goals varied with each sub-study. The interaction in the studies mentioned here focused on the StOEH, members of the steering committee and GPs. The policymakers at the ministry did not interact with the researchers in the beginning of the research period but became involved towards the end, when the results were discussed.

Our analysis of the prevalence of hypercholesterolaemia among screened persons showed that 17% of FH+ persons did not have hypercholesterolaemia. The StOEH received this with some reluctance, as this was perceived as a rather high percentage. The very first response to our finding was, 'Your data are wrong.' (Actually, the data had been obtained from the StOEH database.) This response may have been the result of the difference between our findings and the assumptions of the staff involved in executing the screening programme. The policy document for the screening programme stated: 'FH is a disease that is probably 100% penetrant' [7]. Our findings challenged the statement about the penetrance of the LDL receptor gene mutations and stressed the importance of measuring serum cholesterol levels

in addition to a DNA analysis. By working closely together with the initiators of the StOEH on the research paper presented in Chapter 2, we could present our results of the analysis of the StOEH database, point out the importance of more research about the genotype-phenotype mechanisms in FH and at the same time facilitate constructive cooperation between the health services researchers and those involved in the StOEH.

During the study of the second additional question (What proportion of patients with FH were identified with hypercholesterolaemia in general practice prior to genetic screening?), the interaction of the health services researchers (including the medical student) focused on GPs. We experienced good cooperation and GPs expressed interest in the findings of the study. The contribution from the GPs was limited to allowing access to their patient records, which was very often facilitated by their practice assistants.

The interaction during the exploration of the third additional question (What is the potential of the current methodology of pedigree analysis and follow-up: How many family members can be reached by the programme and how many have already been reached?) proved more difficult. As analysis of the genealogic information (collected and owned by the StOEH) was not perceived by the StOEH as being part of the initial research question, the StOEH had to approve of this study in a separate decision-making process. Sharing this confidential information with a third party (health services researchers) needed utmost consideration. A document in which we presented the importance of the analysis for the evaluation of the programme and in which we proved to be able to transform a confidential, family-specific database into an anonymous database failed to persuade the StOEH [8]. The StOEH decided not to approve this study on legal grounds (the informed consent did not cover linking pedigree information and DNA diagnoses) and quality grounds (the pedigree database could not be guaranteed to be of sufficient quality for the analysis). After intensive communication and explanations, we had to abandon the plan to study this aspect of the screening programme [9]. The student graduated with a thesis on the theoretical approach of the pedigree analysis and the analysis of a test database that contained a mock family tree [2].

Studying the consequences of screening when applying for insurance (additional research question 4) was well received by both the StOEH and policymakers. A patient-support organization dealing with issues related to insurance and labour contributed to the study [10]. This organization provided data on the number of complaints their help-desk had received regarding genetic testing and applying for insurance in the years prior to our evaluation. The study showed (data not shown in this thesis) that participants of a genetic screening programme still encounter unanticipated insurance problems. It is not clear why these problems occur: whether insurance companies ask questions regarding genetic testing or questions that can be interpreted as such, or whether individuals themselves give more information than they have been asked for. The researchers concluded that guidelines and legislation on genetic information are just a prerequisite and that education of all those involved is equally important [3].

The interaction with the StOEH and its initiators was most explicit when studying the cost effectiveness of the screening programme, the content question in this case (Chapter 4). Whereas the screening programme was developed and implemented from the perspective

of microbiologists and internal medicine specialists, the evaluation study was developed from the perspective of public health (rather than the health of the individual patient): what are the costs and effects for the total population, the population of screened persons and the population of persons at risk of having familial hypercholesterolaemia? We consequently chose what health economists call the societal perspective for the cost-effectiveness analysis [11]. Our technical approach of the analysis was debated by those involved in the StOEH. To create an opportunity to discuss the findings, a workshop was held at the initiative of ZonMw [12]. Horstman [13] studied the evolvement of the debate on the implementation of the screening programme and she stressed the importance of the different perspectives from the involved actors, including our health services research group and the StOEH. This difference is also shown in another cost-effectiveness study of the same screening programme published by a group of researchers from the UK and the StOEH [14]. Their analysis showed a cost of $8,700.00 per life year gained, compared to $32,000.00 in our study. (At the time, the exchange rate for dollars to euros was 1:1.) In both analyses, the risks of cardiovascular disease mortality were modelled using different studies on which these models were based. As a consequence, neither of the two cost-effectiveness analyses represents 'reality'. The difference between the two cost-effectiveness ratios is primarily based on three factors. Firstly, in our study we chose a population model (based on persons from the general population with unknown FH status) for calculating the risk of cardiovascular disease (CVD) mortality [15]. Wonderling et al. chose a model based on the mortality risk in a cohort of clinically diagnosed FH patients (with clinical symptoms of hypercholesterolaemia) documented in the Simone Broome Register [16]. This resulted in a lower risk estimation and fewer life years gained in our study. Secondly, we estimated the costs of treatment till the age of 85 instead of 60, as in the study by Wonderling et al. This led to a higher estimated cost of treatment in our study. Thirdly, we included the costs of diseases (other than CVD) that would occur in the life years gained after the screening. This debate of perspectives, methods and techniques, including the cost-effectiveness publications and an accompanying editorial [17], indicates not only that evaluation perspectives differed, but also that actors are convinced that scientific arguments contribute to the decision-making process on the funding and continuation of the programme.

Follow-up of events and developments

Several developments have occurred since the publication of the evaluation report [5] and the workshop on the evaluation results [12]. Firstly, the results from the study on getting insurance after screening for FH [18;19] received much attention in the media (e.g. [20;21]) and led to questions being asked in parliament [22;23]. As a result, the minister for Health, Welfare and Sport initiated further investigations by the Health Council of the Netherlands [24;25] and delayed the decision on continuation and expansion of the screening programme [26]. Depending on agreement with the insurers about the protocol for insuring FH patients [27], the minister decided that although the costs per life year gained were high (as we had shown), the importance of avoiding the health effects of FH weighted heavier. Therefore,

the decision was taken to continue the programme and incorporate it into the general health care package covered by the Dutch Sickness Fund [27]. The Health Care Insurance Board (CVZ) was appointed to coordinate the nationwide implementation of the programme. A scientific expert committee was appointed to advise the CVZ [28].
Secondly, in December 2004 the CVZ defined an additional evaluation of the acceptability of the programmes' approach, and of the potential negative consequences of a genetic diagnosis on obtaining insurance [29]. These evaluation studies were carried out in 2005 [30].
Thirdly, the importance of further studying the risk for cardiovascular disease in persons with a genetic mutation for the LDL receptor gene but without an increased LDL level was formulated by the Health Council of the Netherlands [25], supporting our findings presented in Chapter 2 [1].
Fourthly, based on the findings of our evaluation, we recommended considering the inclusion of the treatment of FH in the new clinical practice guidelines on cardiovascular risk management for GPs [31]. Attempts to achieve this led to a separate publication of a specific guideline for diagnosis and treatment of FH [32] and a position statement regarding this issue from the Dutch Association of General Practitioners NHG [33].
In 2005, the coordination of the screening for familial hypercholesterolaemia was transferred from the CVZ to the National Institute for Public Health and the Environment (RIVM), where the coordination of all national screening and prevention programmes is positioned [34]. It is unclear whether this shift in coordination leaves the follow-up of the recent evaluation results [30] as well as the overall scientific guidance of the screening programme in a vacuum.
In conclusion, the developments regarding FH screening in the Netherlands show that the issue is no longer whether or not a family- and DNA-based screening is desirable, but rather how the conditions under which the programme is implemented can be redesigned. With the transfer of the coordination of the screening programme from the research-based StOEH to the Health Care Insurance Board and again to the RIVM, the screening programme (and the discussion about it) has been put firmly into the domain of public health services. Our health services research has contributed to this evolution by producing relevant scientific knowledge, by interaction and by open debate with other scientists and involved actors. Several results of our efforts have been incorporated into the policymaking process, which led to the health minister's decision to expand the screening programme, continue its evaluation and encourage further research.

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