2017

REPORT

KNOWLEDGE GAPS

Research gaps identified in systematic reviews and health technology assessments published by the Norwegian Knowledge Centre for the Health Services in 2015

Norwegian Institute of Public Health

Title	Research gaps identified in systematic reviews and health technology assessments published by the Norwegian Knowledge Centre for the Health Services in 2015
Norsk tittel	Kunnskapshull identifisert via systematiske oversikter og metodevurderinger publisert av Nasjonalt kunnskapssenter for helsetjenesten i 2015
Institusjon	Division for Health Services (previously Knowledge Centre) at the Norwegian Institute of Public Health
Ansvarlig	Camilla Stoltenberg, direktør
Forfattere	Vist, Gunn Elisabeth *Seksjonsleder, Kunnskapssenteret i Folkehelseintituttet* Fure, Brynjar *Seksjonsleder, Kunnskapssenteret i Folkehelseintituttet*
ISBN	978-82-8082-853-8
Publikasjonstype	Report 2017
Antall sider	37
Oppdragsgiver	Norwegian Institute of Public Health
Emneord(MeSH)	Knowledge gaps, research waste
Sitering	Vist GE, Fure B. Research gaps identified in systematic reviews and health technology assessments published by the Norwegian Knowledge Centre for the Health Services in 2015. Report 2017. Folkehelseinstituttet –2017. Oslo.

Norwegian Institute of Public Health
Oslo, June 2017

Key messages

Title: Research gaps identified in systematic reviews and health technology assessments published by the Norwegian Knowledge Centre for the Health Services in 2015

Publisher

Norwegian Institute of Public Health

The Division for Health Services (previously the Norwegian Knowledge Centre for the Health Services) in the Norwegian Institute of Public Health publishes an annual report of the knowledge gaps that we have identified during our work with systematic reviews and health technology assessments (HTA). The identified gaps in this report relate to issues we have been commissioned to assess in 2015, but they cover of course just some of the gaps in health and welfare nationally and internationally.

Twenty-four of our 30 systematic reviews and HTAs published in 2015 concluded that there is a need for more and better research. There is also a need for more systematic reviews and updates of existing reviews. This includes questions regarding public health, oral health, screening, vaccine, pharmaceutical technologies, medical devices, complex interventions in hospitals, patient safety programs, eating disorders, chronic illnesses, organisation of care and welfare interventions.

Based on the reports published in 2015, there is a need for studies that directly compare relevant interventions, studies that report on important outcome measures, and studies with longer follow up periods. An identified knowledge gap does not necessarily imply that new research should be initiated. We should always consider need for research in connection with other information.

Hovedfunn

Område for helsetjenester i Folkehelseinstituttet (tidligere Nasjonalt kunnskapssenter for helsetjenesten) publiserer årlig en oversikt over kunnskapshull som vi har identifisert gjennom arbeidet med systematiske oversikter og metodevurderinger. Dokumentasjonsgrunnlaget i oversiktene skal bidra til kunnskapsbaserte beslutninger i helse- og velferdstjenester i Norge. Kunnskapshullene som er identifisert er knyttet til spørsmålene som vi har fått i oppdrag å vurdere i 2015, men de dekker selvfølgelig bare noen av kunnskapshullene innen helse- og velferdsfag nasjonalt og internasjonalt.

Av 30 oversikter som ble publisert av oss i 2015, konkluderte 24 med at det er behov for mer og bedre forskning om effekt av tiltakene som ble vurdert. Det er også behov for nye systematiske oversikter og oppdatering av eksisterende. Dette gjelder for spørsmål innen folkehelse, munn/tann-helse, farmasøytiske intervensjoner, medisinsk utstyr, sammensatte tiltak i sykehus, pasientsikkerhetsprogram, spiseforstyrrelser, kroniske tilstander, organisering og velferdstiltak.

Basert på rapportene publisert av Nasjonalt kunnskapssenter for helsetjenesten i 2015 er det behov for studier som direkte sammenligninger effekten av relevante intervensjoner, studier som rapporterer de viktige utfallsmålene, og studier med lengre oppfølgingstid. Identifisering av et kunnskapshull innebærer ikke nødvendigvis at ny forskning skal igangsettes. Forskningsbehov må alltid ses i sammenheng med annen informasjon.

Tittel:
Kunnskapshull identifisert via systematiske oversikter og metodevurderinger publisert av Nasjonalt kunnskapssenter for helsetjenesten i 2015

Hvem star bak denne publikasjonen:

Folkehelseinstituttet

Table of contents

Introduction

The Division for Health Services (previously the Norwegian Knowledge Centre for the Health Services) in the Norwegian Institute of Public Health publishes systematic reviews and health technology assessments that answer questions about effect, safety, cost effectiveness, experiences with interventions, and organisational, ethical or legal consequences of interventions on behalf of health and welfare services in Norway. The aim of our reviews is to contribute to informed decisions so that users, including patients, receive the best possible services.

The questions that are answered in our reviews do by no means cover all needs and questions that services need answers to, but they cover questions that we have received through our proposals and commissioning processes.

The four main channels for commissions are:

- the Ordering Forum in the National System for Managed Introduction of New Health Technologies in the specialist health services in Norway (www.nyemetoder.no)
- the The Division for Health Services (previously Knowledge Centre) in the Norwegian Institute of Public Health 's own proposals and prioritization process. The center's prioritization forum, which is composed of representatives from health authorities, community health services, professional associations and patient associations helps us to prioritize which of the suggested questions that we answer every year
- the Secretariat for National Guidelines at the Norwegian Directorate of Health propose questions for systematic reviews tailored to aid ongoing guideline processes
- the Unit for social research's proposal and prioritization process. Five welfare directorates – the Norwegian Labour and Welfare Administration, the Norwegian Directorate for Children, Youth and Family Affairs, the Norwegian Directorate of Health, the Directorate of Integration and Diversity, and the Norwegian State Housing Bank – may suggest reviews twice a year. A coordination group, composed of representatives from each of these five directorates, prioritizes the suggested reviews.

This report summarizes the knowledge gaps we have identified in our 30 systematic reviews and health technology assessments that we published in 2015.
Our systematic reviews and health technology assessments contain either a systematic review of individual studies (primary studies) or a (systematic) overview of reviews. The health technology assessments additionally include a health economic evaluation, and/ or an assessment of organizational, legal and ethical consequences. We only conduct a systematic review of primary studies where there is not already a relatively up-to-date one of high quality available.

A systematic review may conclude about future research needs for primary studies, or reveal when there is sufficient information available.

In an overview of reviews, we only search for systematic reviews. Therefore, it can be difficult to comment on the need for new primary studies. New studies may have been published since the search in the reviews were conducted. Overviews of reviews comment only on the need for systematic reviews or the need to update existing ones.

Systematic reviews can conclude that an intervention has a clear effect or risk of injury, or as is often the case, that the research does not create sufficient basis for clear conclusions. Sometimes we conclude that there is a complete lack of research on the effect of important interventions. They are all important in the assessment of which new research is needed, for example as a basis for financing new research. Where reviews show that there are clear conclusions about the effectiveness of interventions, it is an equally important signal that there is no need for more research on exactly this question.

In general, all research, both research involving humans and animals, should take place in light of how much, or how little research that already exists about the current question. The principle of "evidence-based research," that new studies are rooted in the sum of previous research, helps to reduce avoidable waste in research and this now receives increasing attention. A network of evidence-based research is established: ebrnetwork.org. (1, 2).

When available research does not provide sufficient grounds to form clear conclusions, it may be the result of a lack of research on the intervention in question, or available research has been unsatisfactorily performed. Or, as we often find, the research is reported incompletely or so poorly that it is difficult to interpret and use as a basis for conclusions.

There is an international consensus that it is useful to connect the scientists who write systematic reviews and HTAs and thereby identify gaps in knowledge with scientists who actually do the research, and not least connect, with those who finance

research.

There is an increasing proportion of funding internationally that is being earmarked to targeted research, for example in PCORI and the large Health Technology Assessment (HTA) Programme in UK (http://www.nets.nihr.ac.uk / Programmes / hta). The programs are set up to commission research based on identified knowledge gaps. The Ministry of Health and Care Services indicates that this will be a focus for research funding in Norway too.

The results in systematic reviews are often based on international research with few of the studies carried out in Norway or the Nordic countries. Thus, there is often uncertainty about the transferability of the results and uncertainty whether we can expect the same effect as in the studies if the intervention is implemented in Norway. This is particularly a difficult assessment in terms of the effect of organizing of services and health economic evaluations as we have some unique organizational systems in Norway.

For many interventions, it may be difficult to perform large enough studies, especially in countries with small populations such as Norway. There is a need for more research support both nationally such as NORCRIN (http://www.norcrin.no) and internationally, such as ECRIN (http://www.ecrin.org) for Europe. As part of the cooperation on HTA in Europe through EUnetHTA Joint Action 2 has established a database of recommendations on further research needs: EVIDENT database, see www.eunethta.eu.

We have compiled the knowledge gaps that our systematic reviews and HTAs published in 2015, have identified. We should always consider the need for research in Norway in connection with other information. Therefore, we have presented both the main findings regarding the questions that we have considered, and the knowledge gaps.

Methods

We have gathered information about knowledge gaps from the 30 systematic reviews and health technology assessments that the Norwegian Knowledge Centre for the Health Services (currently the Division for Health Services in the Norwegian Institute of Public Health) published in 2015.

Our systematic reviews, overviews of reviews and HTAs include a section entitled: "Identified research gaps". We have collected information from this section as well as other places in the reports.

We present the information from these reviews in the text.

Results

In 2015, the Norwegian Knowledge Centre for the Health Services (currently the Division for Health Services in the Norwegian Institute of Public Health) published 30 systematic reviews and health technology assessments in response to assignments from the Norwegian health and welfare services. We have compiled information on the knowledge gaps identified in these systematic reviews. First, we present the knowledge gaps thematically and then we list methodological research needs that we have identified.

Public health

Three reviews referred to public health. One systematic review of primary studies assessed the effect of information and communication strategies targeting physical activity and one or more lifestyle changes (3). The other systematic review of primary studies assessed the effect of infectious control interventions in day care facilities (4). The overview of reviews assessed interventions considered relevant for the updating of a national guideline for mother and child health centers, interventions include home visits and parent education/ guidance and counselling (5).

Information and communication strategies targeting physical activity and one or more lifestyle changes

This systematic review included 79 comparisons (from 75 studies) conducted in 22 different countries. The main conclusion of this systematic review was that information and communication strategies had beneficial effects for certain outcomes with short-term follow-up when compared with the control group who did not receive the intervention. At long-term follow-up, we found that there was less caloric intake in the intervention group compared to the control group. For other outcomes, there was little or no difference between groups. We assessed the quality of the evidence to be of moderate to very low quality. Based on this documentation, we found little or no effect of population-targeted strategies to promote physical activity compared with a population-targeted interventions to improve diet (3).

Knowledge gaps – Information and communication strategies targeting physical activity and one or more lifestyle change

- there is a need for more research on population-oriented social and recreational based interventions outside the school and workplace, and on effects of interventions aimed at increasing physical activity in addition to other lifestyle habits
- there is also a lack of knowledge on the effect of interventions aimed at physical activity in addition to one or more lifestyle habits compared with another lifestyle habit, and on interventions aimed solely at physical activity and the effects this may have on other habits
- it is important to plan good evaluations before implementation of new costly population-oriented interventions with uncertain effect, to ensure safe interventions and best use of resources. For most such interventions it will be possible to conduct (Cluster) RCTs, but interrupted time series evaulations and non randomised studies may also be suitable where randomized trials are not possible for practical reasons
- preventive public health measures require long-term follow-up, since it may not be possible to observe all beneficial effects and side effects until after a certain time
- further, any effects (advantage and disadvantage) should be weighed against the resources needed to implement such complex interventions. There is also a lack of knowledge about the costs of such interventions. This should be included in future evaluations
- we identified only indirect or subjective measures of health. Future evaluations should aim to measure the effects on the population with direct measures of health

Infection control in day-care facilities: Effect of hand hygiene, training and physical interventions

The main conclusions from this systematic review were that attention to hand hygiene practice compared to practice as usual reduces children's incidence of diarrhea, reduces respiratory tract infections, and reduce absenteeism rates. The evidence was of moderate to low quality. A complex intervention that combined practical hand hygiene with training and facilitating hygiene routines reduces the incidence of diarrhea, respiratory tract infections, the number of physician consultations, and the prescription of antibiotics to children. The intervention also has advantages for day-care facility staff, and it reduces parents' absenteeism. The evidence was of low quality (4).

The effectiveness of initiatives concerning physical conditions (occupation density, time spent indoors/outdoors, space, ventilation, etc.) was uncertain. The documentation was of very low quality. This does not mean that the interventions do not work, but that the current scientific evidence lacks power to conclude about their effect (4).

Knowledge gaps - Infection control in day-care facilities

- given the lack of primary studies on the effectiveness of initiatives concerning physical conditions such as occupation density, time spent outdoors, and space in day-care facilities, there is a need for additional, well-planned RCTs
- relevant outcomes include prescription of antibiotics, resistance to antibiotics, absenteeism for children, parents and staff

Mother and child health centers

This overview of reviews assessed interventions considered relevant for the updating of a national guideline for mother and child health centers, interventions included home visits and parent education/ guidance and counselling. The main conclusions were that multiple home visits possibly increase maternal satisfaction after seven months, possibly lower the use of health services for the child, and more children receive exclusive breastfeeding at six weeks than after just one home visit. Parent Training (45 minutes consultation with a health worker) possibly leads to a few minutes more sleep per day and per night. Parent Training on proper sleeping position possibly increases correct sleeping position after three and six months. Training to promote smoking cessation in pregnancy and the neonatal period possibly increases the number of parents who do not allow smoking indoors. Day-care Program together with parent education about motor development possibly increases children's motor skills. This evidence was of low quality and we have limited confidence in these results (5).

Research gaps- Mother and child health centres

Research regarding the following interventions was too sparse to conclude so we still lack research regarding:

- maternal and child mortality, and the incidence of respiratory infections after one home visit compared with multiple home visits
- parent Training by disseminating information to new parents about sleep
- parent Training on infant's overall health
- parent Training about babies security. We have too little available information about securing infants in cars and about temperature testing of bath water
- parent Training, both with and without given information, and tailored programs for smoking cessation
- parent training on small-child behaviour

Oral health

Three systematic reviews of primary studies referred to oral health. One systematic review of primary studies assessed the effect of fluoride varnish for children under three years old (6). The second one compared the effectiveness of first oral examination in children 0 to 2 years with first oral examination in children 3 to 5 years old (7). The third systematic review assessed the effect of educating and counselling parents with pre-school children (8).

Fluoride varnish for children under three years old

The main conclusion from nine randomized controlled trials was that fluoride varnish probably reduced caries in milk teeth, and that fluoride varnish might have few or no side effects or other adverse events. There was no information about infections or poisoning (6).

Knowledge gaps - Fluoride varnish for children under three years old

- there is no need for more studies on the caries preventive effect of fluoride varnish

Dental and oral examination of children 0 to 5 years

This report is about effects of a first dental and oral examination in children 0-2 years compared to a first dental and oral examination in children 3-5 years regarding prevention of dental caries. We did not find studies that directly answered our question (7).

Knowledge gaps- Dental and oral examination of children 0 to 5 years

- several high quality studies with enough participants are needed. It is desirable and possible to carry out randomized controlled trials. In addition to outcomes related to caries, outcomes such as costs associated with the intervention as well as harms (e.g. anxiety in children or guardians connected to the examination) should be investigated
- another area of interest is possible effects of how the intervention is organised, e.g. whether results differ if the intervention is given by dental health personnel or primary health care personnel

Parent education on ways to prevent dental caries in pre-school children

In all the studies summarized in this systematic review, the parents received education and counselling regarding dietary habits and dental hygiene practices that promote good oral health. However, both the educational content, the strategy used and the number of sessions varied considerably. The main conclusions were that children of parents that received recurrent education and counselling sessions had somewhat improved short- and long-term oral status compared to children of parents who did not have this opportunity (8).

The majority of the studies compared giving comprehensive education and counselling with giving the parents only some education, advice, or information. These studies had inconsistent findings. Based on these findings, we could not conclude whether some education and counselling strategies were more effective in preventing childhood dental caries. Most of the studies were conducted in population groups where early childhood dental caries was prevalent and among vulnerable groups of parents. It can be especially difficult for these parents to change behaviours and habits (8).

We found four protocols for relevant studies that were in progress. All these studies were looking at the effects of using motivational interview in parental guidance for preventing caries in young children, alone or in combination with other components. When these studies are published, it will be appropriate to conduct a systematic review on the effect of motivational interview.

Knowledge gaps - Parent education on ways to prevent dental caries in pre-school children

New studies should:

- make a distinct difference between the content in the intervention and the control group
- be of sufficient size to be able to show any effects of the intervention
- include detailed descriptions of how training and supervision takes place and theoretical foundation of strategies

Screening

Two systematic reviews of primary studies assessed screening tools. One provided an overview of existing cognitive screening tests for assessing functions of relevance for ability to drive a car, and how good the tests are for predicting who will pass an on-road driving test or who will experience a car accident during the first years after the screening test (9). The other one conducted a psychometric assessment of the

Clock Drawing Test, which is a screening instrument for measuring cognitive impairment (10).

Screening tools for cognitive function and driving

This systematic review evaluated which cognitive screening tests that are valid and reliable instruments for predicting whether cognitive functioning is sufficient for safe driving. We searched systematically for tests that have reported diagnostic study test accuracy for cognitive screening tests designed to predict results on standardized driving tests. In total, we identified 53 studies that fulfilled our inclusion criteria. Of these, 47 compared results from a cognitive screening test with results from an on-road test. Three studies had a simulator as reference test, whereas three studies had both simulator tests and on-road tests as reference tests. Three studies reported diagnostic accuracy for the Trail Making Test A and B in and two studies reported diagnostic accuracy for the Montreal Cognitive Assessment. All other studies used different combinations of outcomes. There was a large variability for diagnostic accuracy of different tests across studies. The quality of evidence ranged between low and very low. The most obvious challenge in this field is the lack of standardization of tests used in research. In addition, we found no studies that had used traffic accidents as outcome (9).

Knowledge gaps - Screening tools for cognitive function and driving

- there is a need for standardization of the outcome measures and the test batteries in research about screening tests for driving ability

Psychometric assessment of the Clock Drawing Test

The Clock Drawing test is a screening instrument for measuring cognitive impairment. The test has been in use since the 1950-ies, and from 2012 a Norwegian version exists. In the most commonly used version of the clock drawing test, the tested person is instructed to draw a round clock circle with one short and one long arm facing toward a given time point. We assessed research on psychometric properties of the Clock Drawing Test. We identified three systematic reviews that fulfilled our inclusion criteria, none involving Norwegian patients. Even though the Clock Drawing Test showed good to excellent diagnostic accuracy, it encompasses only some aspects of cognitive functioning, and should be used in combination with other tests. In addition, different versions and scoring systems are available for the Clock Drawing Test. We did not find studies that compared the diagnostic properties of different versions (10).

Knowledge gaps - Psychometric assessment of the Clock Drawing Test

- there is a need for comparative studies about the different clock drawing tests so that the test with the best psychometric properties is identified

- there is a need for more research so that it may eventually be possible to arrive at a consensus on how the test should be administered and scored

Vaccine

One systematic review of primary studies assessed the effect of vaccination (11) and one cost-effectiveness assessment looked at HPV-vaccination of boys aged 12 in a Norwegian setting (12).

HPV-vaccination of boys

Human papillomavirus (HPV) is the most common sexually transmitted agent worldwide and more than 100 types of HPV have been identified. This systematic review assessed whether vaccinating boys with the same HPV vaccines currently offered to 11 to 12-year-old girls in Norway would be effective in preventing HPV-related diseases among males. HPV vaccine is efficacious in preventing external genital lesions with infection of HPV 6, 11, 16 and 18 in boys and men aged 16-26 years. The main genital lesion prevented is genital warts. There were very sparse data on precancerous lesions (PIN2+) and the results were so far not conclusive with 3 years follow up. HPV vaccination reduced the risk of anal intraepithelial neoplasia (AIN2+) in a subpopulation of men who have sex with men. There was little or no difference in the occurrence of serious adverse events when compared to the control groups. The present systematic review found no results for the effects of the vaccine on the incidence of penile or anal cancer or cancer-related mortality (11).

Knowledge gaps - HPV-vaccination of boys

- long-term follow-up studies are needed to assess if there is an effect of HPV vaccination on cancer outcomes
- long-term follow-up studies could also generate more data on the safety aspects of the vaccine
- the following research question for long-term studies to demonstrate effects on cancer incidence, cancer-related mortality and safety is suggested:
    - design: Prospective observational studies (vaccinated versus non-vaccinated cohorts) and registry studies
    - population: Male vaccination age 10-16 years
    - intervention and comparator: HPV vaccines versus placebo or other vaccines
    - outcomes: Cancer related mortality, penile cancer, anal cancer, oropharyngeal cancer other cancer types, pre-cancerous lesions unrelated to HPV status in the lesions, serious adverse events
    - international collaboration is essential in order to generate sufficient data and avoid duplication of work

Cost-effectiveness assessment of HPV-vaccination of boys

This economic evaluation examined the cost-effectiveness of vaccinating both 12-year-old boys and girls against HPV-infection compared to maintaining the current practice of vaccinating only 12-year-old girls. The main finding of the evaluation was that from a societal perspective, vaccinating boys in addition to girls aged 12 with the quadrivalent vaccine is probably not cost-effective. The incremental cost-effectiveness ratio (ICER) was NOK 1,626,261 for a quality-adjusted life-year (QALY).

Although there is no official cost-effectiveness threshold value in Norway, such high ICERs are generally associated with the intervention not being accepted for implementation in the Norwegian health sector.

Knowledge gaps: cost-effectiveness assessment of HPV-vaccination of boys

- there is a need for more EQ-5D data of high quality on the HRQoL of HPV-related outcomes as well as Norwegian general population data with the EQ-5D instrument

Pharmaceutical technologies

Four reviews looked at pharmaceutical technologies, two systematic reviews of primary studies and two overviews of reviews. One systematic review of primary studies assessed new drugs for inoperable or metastatic malignant melanoma (13), the other one assessed use of naltrexone in low doses beyond the approved indication (14). One overview of reviews assessed the use of aminoglycosides for treatment of sepsis (15). The other overview of reviews assessed maintenance treatment with antipsychotic drugs for people with schizophrenia (16).

New drugs for inoperable or metastatic malignant melanoma

This health technology assessment of primary studies compared the relative effectiveness and cost-effectiveness of seven new drugs used for the treatment of advanced malignant melanoma patients in the Norwegian setting. The drugs were: cobimetinib, dabrafenib, ipilimumab, nivolumab, pembrolizumab, trametinib and vemurafenib. The clinical endpoints are overall survival, progression-free survival, health-related quality of life and serious adverse events. Conclusions from network meta-analyses (including 17 randomized controlled trials) used both direct and indirect evidence with dacarbazine as a common comparator. The different treatments were ranked in terms of their likelihood of leading to the best results for each endpoint (13).

None of the interventions were cost-effective at the maximum pharmacy retail prices, and the budget impact if the interventions are accepted in clinical practice

are substantial. Drug price reductions in the region of 63 to 84 percent would be necessary to improve the cost-effectiveness and reduce the budget impact. The sensitivity analysis showed that the clinical effectiveness data is the most influential source of uncertainty, followed by health-related quality of life data, costs and the relative risks for serious adverse events (13).

Knowledge gaps – New drugs for inoperable or metastatic malignant melanoma

- there is a need for studies to confirm the results in the studies that are already available
- there is a need for studies to compare the interventions directly
- there is a need for studies on subgroups of the advanced malignant melanoma population
- there is a need for studies on health related quality of life
- there is a need for longer-term trials both for monotherapies and combination therapies for efficacy
- there is a need to follow development of resistance for the BRAF-inhibitors and safety
- there is a need for studies on optimal treatment time for the different drugs and combination of drugs
- there is a need for studies on the optimal sequence of the alternative treatments
- there is a need for studies on combination of drugs with different mechanisms of actions

Use of naltrexone in low doses beyond the approved indication

In Norway, naltrexone is approved as supportive treatment of alcohol dependence. The recommended dose is 50 mg, equivalent to the marketed tablet. Naltrexone in much lower doses than 50 mg has been used in Norway for the treatment of a variety of diseases, such as multiple sclerosis (MS), Crohn's disease, fibromyalgia, cancer, inflammatory bowel disease, chronic fatigue syndrome, and amyotrophic lateral sclerosis. Doses of 3 to 5 mg per day have often been termed low-dose naltrexone. This use is beyond the approved indication. This systematic review of primary studies examined whether there is a documented effect of the use of naltrexone in low doses. All studies were either small, of short duration or had other methodological limitations. We considered the evidence to have very low quality. That means that we cannot conclude whether the use of naltrexone in low doses is effective or safe. In the included studies, low-dose naltrexone was mainly used as add-on to the patient`s ordinary treatment. In our opinion, the outcomes that we studied i.e. change in the course of the disease and effects on daily functioning, are among the most important outcomes for patients (14).

Knowledge gaps - Use of naltrexone in low doses beyond the approved indication

- as the mechanism of action for naltrexone is not fully understood, it may be difficult to identify the most relevant time frame for studies. It may be relevant to perform shorter studies with a time frame that can uncover potential effects followed by longer studies to evaluate clinical effectiveness and safety of naltrexone
- there is a need for well-planned and well-conducted RCTs of long enough duration to reliably capture any effects
- there is a need for long-term studies to investigate whether effects persist over time
- there is a need for studies that assess if side effects occur during long-term use
- this research question is relevant for many countries, and international studies across several countries could increase power

Aminoglycosides for treatment of sepsis

Sepsis is a potentially dangerous or life-threatening medical condition, usually caused by a bacterial infection. In Norway, sepsis is usually treated with antibiotics, and a typical regimen could be to use a narrow-spectrum antibiotic, for example a beta-lactam antibiotic such as benzylpenicillin in combination with a highly potent, broad-spectrum antibiotic, such as an aminoglycoside. This overview of reviews looked at treatment effects and harms of any antibiotic regimen with an aminoglycoside versus any antibiotic regimen without an aminoglycoside, for sepsis in adults. Results indicated that beta-lactam-aminoglycoside combination therapy might increase the risk of nephrotoxicity compared with monotherapy. The combination therapy probably leads to more treatment failures compared with beta-lactam monotherapy in adult patients. For overall mortality and serious adverse events, there may be little or no difference between monotherapy and combination therapy. The confidence in the estimates for overall mortality, nephrotoxicity and serious adverse events are limited and the true effect may be different from the estimate (15).

Knowledge gaps - Aminoglycosides for treatment of sepsis

- there is a lack of high quality systematic reviews evaluating the effect of aminoglycoside regimens other than in combination with a beta-lactam antibiotic. We searched for systematic reviews, and cannot tell whether there also is a need for conducting primary studies on the effect of other aminoglycoside regimens than we have presented in this overview of reviews.

Maintenance treatment with antipsychotic drugs for people with schizophrenia

Antipsychotic drugs are the mainstay of treatment of schizophrenia. This overview of reviews compares the effects of all antipsychotic drugs to placebo for maintenance

treatment, i.e. relapse prevention after the acute phase. Randomized controlled trials since the 1950s have consistently shown that antipsychotic drugs effectively reduce relapses and need for hospitalization. However, some patients gain weight, and there is sedation and mobility issues. There may be little or no changes in suicide, daily function and proportion of people at work (16).

There is no need for more studies or reviews about the effect of maintenance treatment with antipsychotic drugs for people with schizophrenia on the effect on relapse and the need for hospitalization (16).

Knowledge gaps - Maintenance treatment with antipsychotic drugs for people with schizophrenia

- there is a need for systematic reviews of studies with long follow-up time
- there is a need for a systematic review with a network meta-analysis of comparative effectivenes and tolerability of all antipsychotic drugs in schizophrenia (but not on the effectiveness of maintenance treatment of these drugs for patients with schizophrenia)

New health technologies

Two health technology assessments (HTAs) and one overview of reviews evaluated new health technologies. One HTA assessed alternatives of plasma for transfusion to patients (17), and the other one assessed the effectiveness of autologous hematopoietic stem cell transplantation for multiple sclerosis (18). The overview of reviews assessed hyperbaric oxygen therapy in patients with late radiation tissue injury or diabetic foot ulcer (19).

Alternatives of plasma for transfusion to patients

Plasma transfusions are used to stop or prevent bleedings, for instance during surgical procedures or in patients with trauma. This HTA evaluated effectiveness, safety and health economic aspects of different alternatives for plasma for transfusion to patients in Norwegian hospitals. Since the early 1990-ies, Norwegian hospitals have used the solvent detergent plasma Octaplas®. Other plasma alternatives have become available, and the research question for this HTA was if any of these are more effective, safer or more cost-effective than Octaplas®? We identified six RCTs and one non-randomized controlled study on solvent detergent plasma, methylene blue plasma, quarantine plasma and fresh frozen plasma. Meta-analyses was not possible as different products were used in different comparisons. The evidence ranged from very low to low quality. None of the controlled trials reported on safety. However, we identified several hemovigilance reports from France, Finland, Greece and Norway. Data were insufficient to conclude whether there are variations between different

pathogen inactivation methods except for allergies, which seem to occur more frequently in methylene blue compared to the other plasma alternatives (17).

Knowledge gaps - Alternatives of plasma for transfusion to patients

- there is a need for studies on the safety of plasma alternatives for transfusion to patients

Autologous hematopoietic stem cell transplantation for multiple sclerosis

Autologous hematopoietic stem cell transplantation (HSCT) is suggested for a small group of patients with relapsing-remitting multiple sclerosis (RRMS) when pharmacological treatment is ineffective or causes unacceptable side effects. This HTA assessed effect and safety of HCST and evaluated health economic and ethical aspects of introducing this technology in the Norwegian health care system. We identified one very small, randomized controlled trial of limited relevance, one registry study and 21 case series of which eight had included mainly patients with RRMS. We assessed the quality of the evidence as very low for all outcomes except for one outcome (mortality at 100 days) that was of low quality (18).

Knowledge gaps - Autologous hematopoietic stem cell transplantation for multiple sclerosis

- there is a need for randomised controlled studies on the effectiveness of autologous hematopoietic stem cell transplantation for multiple sclerosis

Hyperbaric oxygen therapy in patients with late radiation tissue injury or diabetic foot ulcer

Hyperbaric oxygen therapy (HBOT) is a treatment where the patients breathe 100% oxygen in a pressure chamber. This overview of reviews assessed the effect and safety of HBOT in patients with late radiation tissue injury and diabetic foot ulcers. We included two Cochrane reviews and two RCTs published after the most recent of these reviews. The assessed evidence consisted of 17 RCTs with a total of 1117 patients. Compared to standard treatment, HBOT in treatment of late radiation tissue injury of the head and neck region or diabetic foot ulcers may provide more patients with resolution or improvement of symptoms. For other outcomes or for patients with late radiation tissue injury in other locations we were unable to conclude. The identified studies were small, with few events and with risk of bias. Our confidence in the estimates of clinical effectiveness and efficacy was limited. New studies may change the conclusions (19).

There are some ongoing studies about diabetic foot ulcers, and it may be wise to assess these before considering any new studies about diabetic foot ulcers (19).

Knowledge gaps - Hyperbaric oxygen therapy in patients with late radiation tissue injury or diabetic foot ulcer

- there is a need for larger randomized controlled trials with longer follow-up
- there is a need for standardized outcome measures
- there is a need for studies that capture side effects and unexpected events

Patient safety program

Three overviews of reviews deal with patient safety questions considered relevant when updating informed decisions in the patient safety program in Norway. One overview of reviews is about prevention of falls in institutions (20). The second one is about interventions for reducing the risk of infections with the use of central venous catheters (21). The third one is about the effect of medication reconciliation (22).

Prevention of falls in institutions

The main conclusions from this overview was that multifactorial interventions customised to the particular institution probably will reduce rate of falls in hospitals, but not the number of fallers or hip fractures. Vitamin D supplements for patients with low level of vitamin D will probably reduce the rate of falls in care facilities, but not the number of fallers. Patient education by a dedicated nurse in acute care hospital will probably reduce the rate of falls. The difference of using risk assessment tools compared to nurses' judgment in care facilities is probably small on the rate of falls and number of fallers (20).

Knowledge gaps - Prevention of falls in institutions

- further research on supervised exercise program in both care institutions and hospitals
- further research with controlled randomized studies to strengthen the evidence about multifactorial interventions in both care institutions and hospitals
- additional research evaluating sensor technology to improve response from staff when people with elevated risk begins to rise from bed or chair
- studies that include both the circumstances of the fall in addition to individual risk factors, e.g. assistance with bathroom visits in both care institutions and hospitals
- further trials to test the routine use of tools to identify risk of falls

- further research is needed to test interventions aimed at personnel, and to change the organization where the intervention is given, or the introduction of new health care models

Preventing infections associated with the use of central venous catheters

The main conclusion of this overview of reviews was that use of central venous catheters impregnated with antiseptic or antibiotic agents reduces the risk of catheter related bloodstream infections. All-cause mortality, adverse events, or catheter related topical infection are probably not affected (21).

Knowledge gaps - Preventing infections associated with the use of central venous catheters

- there is a need for longer follow-up time in studies, and for studies comparing lock treatment and systemic antibiotics compared to systemic antibiotics alone
- urokinase (with or without heparin) in the lock compared to heparin alone
- antibiotic and heparin in the lock compared to heparin alone
- intravenous antibiotics prior to insertion of central venous catheter compared to no antibiotics first
- transparent polyurethane dressings compared with gauze and tape
- vena jugularis interna compared to vena subclavian
- vena femoralis compared to vena jugularis interna

Medication reconciliation

The main conclusion from this overview of reviews was that medication reconciliation probably reduces the number of medication discrepancies (22).

Knowledge gaps – Medication reconciliation

- there is a need for a high quality systematic review on the effect of medication reconciliation, information about clinical endpoints

Eating disorders

Two systematic reviews of primary studies considered interventions for people with eating disorder. One systematic review looked for interventions to treat pregnant women with an eating disorder (23). The other assessed treatment of persons who suffer from both an eating disorder and diabetes (24).

Treatment of pregnant women with an eating disorder

The main conclusion from this systematic review was that we found no studies on treatment interventions for pregnant women with eating disorder (23).

Knowledge gaps - Treatment of pregnant women with an eating disorder

- controlled trials to evaluate the effect of treatments for pregnant women with eating disorders
- treatments that are effective in some people with eating disorder (such as group therapy, family therapy, cognitive therapy, admission) could be tested in studies where pregnant women with eating disorders participate

Treatment of persons who suffer from both an eating disorder and diabetes

Relevant interventions include structured treatment with a focus on control of blood sugar and regular meals, and or in combination with psychological treatment. Our main conclusion was that there was too little available evidence to make clear conclusions about the effect of any of the treatments. Nor whether there was different effect on people who suffer different combinations of eating disorder and type of diabetes. For women who both binge eat and have diabetes type 2, weekly group meetings over ten weeks with cognitive behavioral therapy may have a similar effect as weekly group meetings over ten weeks with another psychological therapy. The quality of this evidence was low, and our confidence in the effect estimate was limited. For women with subclinical eating disorders and diabetes type 1 or women who suffer both bulimia and diabetes type 1, weekly group meetings or three months as inpatient with psychoeducation was reported to have an effect. The quality of this evidence was very low, and we have very little confidence in the effect estimates (24).

Knowledge gaps - Treatment of persons who suffer from both an eating disorder and diabetes

- there is a need for more research into effects on treating people who have both eating disorder and diabetes. RCTs are desirable and possible
- we need more research about psychoeducation given in weekly group and hospitalization with intensive treatment program to confirm or disprove the usefulness of these treatments
- there are no studies about the effect of treatment for gestational diabetes and concurrent eating disorder
- there are no studies about the effect of treatment for people who suffer from both anorexia and diabetes or any other combinations of eating disorder and diabetes

Chronic conditions

Only one systematic review of primary studies assessed the effect of interventions for people with chronic disease (25).

Hydrotherapy for persons with musculoskeletal disorders

The systematic review summarised the effects of hydrotherapy (training in warm water) on sickness absence and return- to- work among persons with musculoskeletal disorders, and provided a list of systematic reviews that summarised the effects of hydrotherapy on pain, function and quality of life. Only two studies investigated the effects of hydrotherapy. Both were in combination with another type of training, and either cognitive behavior therapy or an education program that promoted coping strategies. The studies assessed self-reported sick absence during the last week among women with fibromyalgia. The main conclusion is that it is unclear whether hydrotherapy influences sickness absences among women with fibromyalgia or chronic widespread pain (25).

Knowledge gaps – Hydrotherapy for persons with musculoskeletal disorders

- there is a lack of randomised controlled trials that assess the effects of hydrotherapy on sickness absence and return-to-work
- a wide range of patients should be included

Organization of care

Three systematic reviews referred to organization of care. One systematic review of primary studies assessed the effect of same day scheduling of appointments in primary care (26). One overview of reviews assessed the effectiveness of guideline implementation interventions (27). The other overview of reviews assessed the effect of first aid training in schools, workplaces, voluntary organisations and sports clubs (28).

Same day scheduling of appointments in primary care

Same day scheduling is a concept where the principle is that patients get an appointment on the same day that they contact their doctor's office. This means that most of the calendar is open for today's inquiries. Relevant outcomes were wait time, number of list patients, number of appointments made, patient satisfaction, use of emergency services, missed appointments, and continuity of care. The main conclusions were that same day scheduling where most of the calendar is open for today's inquiries compared with traditional scheduling where only a couple of doctor's appointments are not scheduled probably leads to reduced wait time, possibly increases the

number of patients meeting for their appointments and improves continuity of care. It is uncertain whether same-day-scheduling has any effect on the other outcomes. We also compared two versions of same day scheduling, both holding a large portion of the calendar open for today's inquiries. One system kept 75% of the calendar open and the other kept 40-5o% open. It is uncertain whether more or less available hours have different effect on the relevant outcomes (26).

Knowledge gaps - Same day scheduling of appointments in primary care

- new controlled studies could provide more definitive answer on the effect of same day scheduling
- practices that have not yet introduced same day scheduling are encouraged to organize the introduction in such a way that it can be evaluated with a solid study design (studies should have a control group) and preferably with several measurements before and several measurements after the introduction
- it could be possible for municipalities to join a randomized controlled trial or a controlled before and after study

Interventions for implementing clinical practice guidelines

This overview of reviews aimed to to summarize research findings (from systematic reviews) on the effectiveness of guideline implementation interventions. The main conclusions were that implementation interventions such as electronic decision-support, educational meetings, outreach visits, audit and feedback, and tailored interventions probably are effective, but that the size of the effect varies, the effect on clinical practice is most often moderate, and the expected effect on health outcomes is modest. For other interventions, the size of the effect varied considerably across studies, and it is difficult to explain this variation. Consequently, it is uncertain how much these interventions will improve adherence to clinical guidelines. For some measures, such as financial incentives and public release of performance data, evidence is lacking or scarce. We therefore cannot say how effective these types of interventions are (27).

Knowledge gaps - Interventions for implementing clinical practice guidelines

- because there is important uncertainty about the effects of implementation strategies, those responsible for guideline implementation should routinely consider rigorous evaluation as a component of any implementation strategy
- head-to-head comparisons of alternative strategies e.g. by random allocation of clinics, hospitals, municipalities etc. to the alternative strategies could provide useful information. Such cluster- randomised trials have been conducted numerous times, including in Norway

First aid training in schools, workplaces, voluntary organisations and sports clubs

This overview of reviews aimed to to summarize research findings on the effect of first aid training in schools, workplaces, voluntary organisations and sports clubs. The main conclusion was that all of the five systematic review showed that training had a positive effect on lay people's first aid knowledge and skills, at least in the short run. Although over 100 studies were included in the systematic reviews, we could extract data from only a few of the studies. The two relevant studies did not find differences in helping behaviour between participants who had received first aid training and those who had not. One study found that helping behaviour was better among recipients of first aid training focusing on helping behaviour compared to recipients of first aid training only or no training. Three studies showed that those who had performed first aid described it as a positive experience. Due to the limitations of the evidence, we cannot draw any clear conclusions about whether or not first aid training in schools, workplaces, voluntary organisations and sports clubs is effective (28).

Knowledge gaps - First aid training in schools, workplaces, voluntary organisations and sports clubs

- high quality research on the effectiveness of first aid training for lay people is sparse. New larger studies of good quality must be available before we can be more certain about the effect of such training
- new studies should include outcomes such as maintenance of skills over time, survival, outcomes in those receiving first aid, the helping rate and the response time, and the quality of the rendered first aid
- research should also look at the costs of extensive training and whether patient-centered outcomes such as survival and functional ability makes up for these costs

Welfare

One overview of reviews and three systematic reviews of primary studies considered welfare interventions. The overview of reviews considered interventions to help at-risk families with children aged 0-6 years (29). The three systematic reviews of primary studies considered interventions for incarcerated parents and/ their children (30), active labor market programs for immigrants (31), and interventions in residential areas and neighbourhoods to promote social contact, social networks and social support (32).

Interventions for at-risk families with children aged 0-6 years

This report is an overview of reviews that have examined the effects of interventions for at-risk families with children aged 0-6 years. We included nine systematic reviews. The results showed that both psychotherapy for mothers, psychotherapy for mothers and infants, and parent training/guidance improve interaction and attachment between mother and child. Parental training/guidance that is well adapted to the group receiving the intervention seems to have a better effect on child outcomes than more general parenting interventions. Home visits seem to have better effect on outcomes for the child and parents if it is started early, the provider is well trained to assist the relevant families and the intervention is delivered over a period of time and focus on a few challenges rather than a range of challenges. Small financial interventions do not seem promising. A larger amount of money could perhaps have better effect (29).

Knowledge gaps - Interventions for at-risk families with children aged 0-6 years

- there is a lack of knowledge about the effect on interaction and attachment between mother and child; both for mothers with schizophrenia and mothers with other psychological problems or substance abuse. Additionally, there is a lack of systematic reviews about other populations
- there are too few randomized controlled trials about interventions to aid parents who struggle with caring for children, both generally and for parents with mental issues
- it might be useful to assess interventions that include home visits and tailoring to the specific families
- because financial incentives are regularly used, they should be studied

Interventions targeting incarcerated parents and their children

Children with incarcerated parents may be at higher risk than other children for developing behavioural problems and poor mental health. This systematic review addressed the effect of interventions for incarcerated parents and/or their children. We included 22 studies. All the included studies were conducted in the USA. They examined three types of interventions: Parenting interventions, prison nurseries, and support groups for children. Only one study evaluated interventions directed at children with incarcerated parents. The main findings of the report are that it is uncertain whether parenting interventions and prison nurseries have an effect on parenting attitudes and behaviour. It is also uncertain whether parenting interventions, prison nurseries, and support groups for children have an effect on children's emotional and behavioural problems. The studies demonstrated some positive results. For example, parents who received parenting interventions had improved knowledge about childrearing as well as acceptance and empathy for their children (30).

Knowledge gaps - Interventions targeting incarcerated parents and their children

- there is a need for more research, preferably large randomized controlled studies on the effect of interventions for incarcerated parents and their children. Particularly, there is a lack of effect studies on interventions directed at children with incarcerated parents
- there is a lack of effect studies on incarcerated parents and their children conducted in a larger sample of populations, including in a Nordic setting
- there is a lack of studies about the use of active visiting centres, children related outcomes and longer term effects.

Active labor market programs for immigrants

In this systematic review, we summarized the effectiveness of wage subsidies, direct employment programmes and special employment programmes, on employment for immigrants. We found no randomized controlled trials. The findings are from six Nordic registry-based retrospective controlled cohort studies. Wage subsidies possibly increase the probability of employment compared to no programme for unemployed immigrants. Direct employment programmes possibly increase the probability of employment compared to no programme for unemployed immigrants. Special employment programmes do not seem to increase employment compared to no program for unemployed immigrants (31).

Knowledge gaps - Active labor market programs for immigrants

- there is a need for randomized controlled trials investigating the effect of place-then-train-based interventions for immigrants

Interventions in residential areas and neighbourhoods to promote social contact, social networks and social support

This systematic review summarised research on the effects of interventions in residential areas and neighbourhoods to promote social contact, social networks and social support. We included five different interventions in the five included trials. These were: Participation in a mutual help network for elderly residents in "planned housing" (elderly people whose socioeconomic status is low and who are able to live independently in their own apartment); Social network stimulation in a high risk group of middle- aged women; Senior centre group program for increasing social support; Peer counselling for youth; Reconstruction of three streets to a 'street-park'. The main message is that it is uncertain whether interventions in residential areas and neighbourhoods promote social contacts, social networks and social support. The results suggest that there may be some positive effects but also negative effects of such interventions (32).

Knowledge gaps - Interventions in residential areas and neighbourhoods to promote social contact, social networks and social support

- there is a need for more research on the effect of interventions in residential areas and neighbourhoods to promote social contacts, social networks and social support in populations

Research related knowledge gaps

One of our systematic reviews from 2015 concluded without suggesting more research (6):

- there is no need for more studies on the caries preventive effect of fluoride varnish for children under three years old

Two of our systematic reviews identified several relevant ongoing studies, these two concluded with a suggestion to await the result from these studies before deciding whether there is a need for more primary research or systematic reviews (8, 19):

- about parent education on ways to prevent dental caries in pre-school children, four protocols for relevant studies were found that are in progress. All these studies were looking at the effects of using motivational interview in parental guidance for preventing caries in young children, alone or in combination with other components. When these studies are published, there will be a good time to conduct a systematic review on motivational interview
- there are some ongoing studies about hyperbaric oxygen therapy in patients with diabetic foot ulcers and it may be wise to assess these before considering any new studies about diabetic foot ulcers

Research gap for systematic reviews

Four systematic reviews are suggested (15, 16, 16, 29):

- aminoglycoside regimens for treatment of sepsis other than in combination with a beta lactam antibiotic
- maintenance treatment with antipsychotica for people with schizophrenia with long follow-up time
- network meta-analysis of comparative efficacy and tolerability of all antipsychotic drugs in schizophrenia (but not on the effectiveness of maintenance treatment of these drugs for patients with schizophrenia)
- interventions for at-risk families with children aged 0-6 years for other populations than mothers with schizophrenia and mothers with other psychological problems or substance abuse

Research gaps primary studies

Twenty-four of the 30 systematic reviews published by the NOKC in 2015 suggested that there might be a need for further primary research (3, 4, 5, 7, 10, 12, 13, 14, 17, 18, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32).

Longer follow up times

Five of our systematic reviews and HTAs called for longer follow-up times (3, 11, 12, 19, 21):

- for preventive public health measures since beneficial effects and side effects may not be possible to observe until after a certain time after information and communication strategies targeting physical activity in addition to one or more lifestyle habits
- to assess if there is an effect of HPV vaccination of boys on cancer outcomes, and to generate more data on the safety aspects of the vaccine
- on new drugs for inoperable or metastatic malignant melanoma both for monotherapies and combination therapies for efficacy, and to follow development of resistance for the BRAF inhibitors and safety
- for hyperbaric oxygen therapy in patients with late radiation tissue injury there is a need for larger randomized controlled trials with longer follow-up times
- in studies on preventing infections associated with the use of central venous catheters

Comparative effectiveness studies

Three systematic reviews asked for direct comparison between relevant interventions (3, 10, 27):

- the effect of information and communication strategies targeting physical activity in addition to one or more lifestyle habits compared with another lifestyle habit, and on interventions aimed solely at physical activity and the effects this may have on other habits
- about the different psychometric clock drawing tests so that the test with the best psychometric properties is identified
- of alternative strategies for implementation of clinical practice guidelines e.g. by random allocation of clinics, hospitals, municipalities etc. to the alternative strategies

Relevant outcomes

Eight of our systematic reviews and HTAs called for use of directly relevant and patient important outcomes, i.e. less use of indirect measures, and to avoid the use of subjective measures alone (3, 4, 5, 9, 11, 12, 19, 28).

Costs

Three reviews called for more information about financial consequences of the relevant interventions (3, 28, 29):

- information and communication strategies targeting physical activity in addition to one or more lifestyle habits
- first aid training for lay people
- interventions to aid parents who struggle with caring for children

Discussion

In this report, we present knowledge gaps from the 30 systematic reviews and health technology assessments published by the Norwegian Knowledge Centre for the Health Services (currently the Division for Health Services in the Norwegian Institute of Public Health) in 2015. These knowledge gaps are limited to the questions that were prioritized in our forum for prioritization of suggestions, or commissioned by the Ordering Forum of the Regional Health Authorities, the Secretariat for National Guidelines at the Norwegian Directorate of Health or the coordination group for the Unit for social research. The gaps in research knowledge identified in our reviews show the need for studies and information for important decisions in Norway and internationally.

Many of our reviews and HTAs published in 2015 identified knowledge gaps. Because the questions we seek to answer are considered important to the Norwegian health care service, we believe that several of the knowledge gaps identified refer to research that may be useful to conduct. Therefore, it is important to collect these experiences and share them with the agencies that finance and perform research in Norway.

As mentioned in the introduction, one should always base new research on a systematic review showing that there actually is a need to devote resources to clarify the current-prevailing question (1, 2). The Norwegian Knowledge Centre for the Health Services, together with the Centre for Evidence-Based Practice at Bergen University College (33) took the initiative to establish an international network to promote evidence-based research, www.ebrnetwork.org. Researchers, those who finance research, ethical committees and editors of journals can help to promote the principle of knowledge based research.

We distinguish between the need for further systematic reviews and HTAs on one hand and the need for more primary studies on the other. There may be updated systematic reviews without primary studies that answer your question, or the available studies may not provide sufficient basis for concluding. Then there is no need for additional systematic reviews before there are newer primary studies available.

The Ordering Forum in the National System for Managed Introduction of New Health Technologies commissioned five HTAs published in 2015. When health technologies are new and not yet in routine clinical use, one can expect existing research to be scarce. Based on one of these HTAs, i.e. autologous hematopoietic stem cell transplantation in multiple sclerosis (17), the Decision Forum within the system decided not to introduce the technology and encouraged clinicians to perform further research. A study on the effectiveness of autologous hematopoietic stem cell transplantation in MS was granted NOK 20 million by the Regional Health Authorities in Norway in February 2017.

The National System for Managed Introduction of New Health Technologies in Norway states that, if certain criteria are fulfilled, a mini-HTA should be performed before a decision on possible introduction of a new health technology in hospitals. In Norway, hospitals perform mini-HTA involving clinicians, librarians, health economists and methodological expertise. Completed mini-HTAs are published in a national database run by the Division for health services in the Norwegian Institute of Public Health. By December 2015, 30 mini-HTAs were published in the database. Of these, approximately 20% concluded that the technology in question should not be introduced, in many cases due to lack of scientific evidence on effectiveness and safety for the technology.

Inadequate reporting of completed studies is an issue for anyone who wishes to use the information from the studies to make decisions or choices based on this information. The same problem applies to systematic reviews. Part of the challenge can be solved if the authors of primary research include more information in their publications, and guides for this are available (34, 35, 36, 37). Journal editors can request this in the referee processes. There is also an ethical challenge if researchers do not report studies involving the participation of patients in a satisfactory manner. An even broader involvement of patients in earlier stages of the study design and performance will also help to make the research more relevant, and one can possibly avoid the situation where important outcomes are missing from the studies. User involvement in research will increasingly become a requirement in applications and in the implementation of health research in Norway. Regional health authorities have followed up the assignment given by the Ministry of Health on this in a report (38). The Research Council has also followed up on this in its programs.

Twenty-four of our 30 systematic reviews and Health Technology Assessments published in 2015 concluded with a need for more research. This is not so surprising considering the nature of the questions that we addressed. The questions that we assess are often chosen because there is some uncertainty about the effects of the interventions, some variations in practice, the experts disagree, or there are questions regarding whether or not to introduce a new method. The available research is then often limited.

Several of our international partners and sister-organizations carry out similar activities to identify and collect the knowledge gaps internationally. We have described this in one of our previous reports about identified research gaps (39).

References

1. Jamtvedt G, Lund H, Nortvedt MW. Kunnskapsbasert forskning? Tidsskr Nor Legeforen 2014; 134: 10-1.

2. Chalmers I, Bracken MB, Djulbegovic B, Garattini S, Grant J, Gülmezoglu AM, Howells DW, Ioannidis JPA, Oliver S. How to increase value and reduce waste when research priorities are set. Lancet 2014; 383: 156-65.

3. Austvoll-Dahlgren A, Lidal IB, Mosdøl A, Odgaard-Jensen J, Denison E, Vist GE. Effects of campaigns and other communication initiatives on physical activity with one or more other lifestyle habits targeting the general population. Rapport fra Kunnskapssenteret nr. 9 – 2015. ISBN 978-82-8121-954-0 ISSN 1890-1298 .

4. Lidal IB, Berg RC, Austvoll-Dahlgren A, Hval Straumann G, Vist GE. Infection control in day-care facilities: Effect of hand hygiene, training and physical interventions. Rapport fra Kunnskapssenteret nr. 6 – 2015. ISBN 978-82-8121-947-2 ISSN 1890-1298.

5. Vist GE, Denison E, Gundersen MW, Grøgaard J, Hanssen-Bauer MW, Helland T, Hvatum I, Kvalnes A, Mosdøl A, Møllebakken K, Sletten TD, Sommerseth Hansen L, Strømme B, Underland V, Wiggen N, Økland T, Lervik JM. Documentation to inform guideline for mother and child health centres. Notat – 2015. ISBN 978-82-8121-994-6.

6. Dahm KT, Dalsbø TK, Kirkehei I, Reinar LM. Effectiveness of fluoride varnish for children under three years. Rapport fra Kunnskapssenteret nr. 20 – 2015. ISBN 978-82-8121-986-1 ISSN 1890-1298.

7. Denison E, Lidal IB, Strauman GH. Effects of dental and oral examination in children aged 0-5 years. Rapport fra Kunnskapssenteret nr. 25 – 2015. ISBN 978-82-8121-997-7 ISSN 1890-1298.

8. Mosdøl A, Forsetlund L, Straumann GH. Effect of parent education on ways to prevent dental caries in pre-school children. Rapport fra Kunnskapssenteret nr. 24 – 2015. ISBN 978-82-8121-991-5 ISSN 1890-1298.

9. Smedslund G, Giske L, Fleitscher H, Brurberg KG. Screening tools for cognitive function and driving. Rapport fra Kunnskapssenteret nr. 21 – 2015. ISBN 978-82-8121-985-4 ISSN 1890-1298.

10. Smedslund G, Siqveland J, Leiknes KA. Psychometric assessment of the Clock Drawing Test. Rapport fra Kunnskapssenteret nr. 16 – 2015. ISBN 978-82-8121-968-7 ISSN 1890 – 1298.

11. Juvet LK, Sæterdal I, Couto E, Harboe I, Klemp M. Effect of HPV-vaccination of boys. Rapport fra Kunnskapssenteret nr. 1 – 2015. ISBN 978-82-8121-937-3 ISSN 1890-1298.

12. Jiménez E, Torkilseng EB, Klemp M Cost-effectiveness of HPVvaccination of boys aged 12 in a Norwegian setting. Report from Kunnskapssenteret no. 2–2015. Oslo: Norwegian Knowledge Centre for the Health Services, 2015.

13. Pike E, Torkilseng EB, Sæterdal I, Jimenez E, Odgaard-Jensen J, Harboe I, Klemp M. A health technology assessment of the new drugs for inoperable or metastatic malignant melanoma patients. Rapport fra Kunnskapssenteret nr. 22 – 2015. ISBN 978-82-8121-993-9 ISSN 1890-1298.

14. Ringerike T, Pike E, Nevjar J, Klemp M. The use of naltrexone in low doses beyond the approved indication. Rapport fra Kunnskapssenteret nr. 8 – 2015. ISBN 978-82-8121-952-6 ISSN 1890-1298.

15. Sæterdal I, Holte HH, Harboe I, Klemp M. Effect of using aminoglycosides for treatment of sepsis. Rapport fra Kunnskapssenteret nr. 3 – 2015. ISBN 978-82-8121-939-7 ISSN 1890-1298.

16. Dalsbø TK, Dahm KT, Reinar LM. What is the effect of maintenance treatment with antipsychotica for people with schizophrenia? Notat – 2015. ISBN 978-82-8121-958-8.

17. Frønsdal K, Knoph Kvamme M, Stoinska-Schneider A, Giske L, Hval Straumann G, Flesland Ø, Fure B. Alternatives of plasma for transfusion to patients. Rapport fra Kunnskapssenteret nr. 5 – 2015. ISBN 978-82-8121-946-5 ISSN 1890-1298.

18. Giske L, Lauvrak V, Stoinska-Schneider A, Frønsdal K, Kvamme MK., Ormstad S, Fure B. Autologous hematopoietic stemcell transplantation for Multiple Sclerosis. Rapport fra Kunnskapssenteret nr. 23 – 2015. ISBN 978-82-8121-992-2 ISSN 1890-1298.

19. Lauvrak V, Frønsdal KB, Ormstad SO, Vaagbø G, Fure B. Effectiveness of hyperbaric oxygen therapy in patients with late radiation tissue injury or diabetic foot ulcer. Rapport fra Kunnskapssenteret nr. 4 – 2015. ISBN 978-82-8121-945-8 ISSN 1890-1298.

20. Holte HH, Underland V, Hafstad E. Review of systematic reviews on prevention of falls in institutions. Rapport fra Kunnskapssenteret nr. 13 – 2015. ISBN 978-82-8121-963-2 ISSN 1890-1298.

21. Holte HH, Underland V, Hafstad E. Preventing infections associated with the use of central venous catheters. Rapport fra Kunnskapssenteret nr. 19 – 2015. ISBN 978-82-8121-972-4 ISSN 1890-1298.

22. Holte HH, Hafstad E, Vist GE. Overview of reviews on effect of medical reconciliation. Rapport fra Kunnskapssenteret nr. 7 – 2015. ISBN 978-82-8121-948-9 ISSN 1890-1298.

23. Reinar LM, Straumann GH, Myrhaug HT, Vist GE. No effectiveness studies on treatment of eating disorders in pregnancy. Rapport fra Kunnskapssenteret nr. 14 – 2015. ISBN 978-82-8121-956-4 ISSN 1890-1298.

24. Vist GE, Reinar LM, Straumann GH, Wisting L. Treatment of persons who suffer from both an eating disorder and diabetes. Rapport fra Kunnskapssenteret nr. 18 – 2015. ISBN 978-82-8121-970-0 ISSN 1890-1298.

25. Myrhaug HT, Strøm V, Hafstad E, Kirkehei I, Reinar LM. The effect of hydrotherapy for persons with musculoskeletal disorders. Rapport fra Kunnskapssenteret nr. 11 – 2015. ISBN 978-82-8121-960-1 ISSN 1890-1298.

26. Straumann GH, Vist GE. The effect of same-day-access to primary care. Notat – 2015. ISBN 978-82-8121-974-8.

27. Fretheim A, Flottorp S, Oxman AD. Effect of interventions for implementing clinical practice guidelines. Rapport fra Kunnskapssenteret nr. 10 – 2015. ISBN 978-82-8121-959-5 ISSN 1890-1298.

28. Strømme H, Jeppesen E, Reinar LM. First aid training may improve first aid skills. Rapport fra Kunnskapssenteret nr. 29 – 2015. ISBN 978-82-8121-979-3 ISSN 1890-1298.

29. Blaasvær N, Nøkleby H, Johansen S, Berg RC. The effect of interventions for at-risk families with children 0-6 years. Rapport fra Kunnskapssenteret nr. 27 – 2015. ISBN 978-82-93479-03-1 ISSN 1890-1298.

30. Nilsen W, Johansen S, Blaasvær N, Hammerstrøm KT, Berg RC. Effect of interventions targeting incarcerated parents and their children. Rapport fra Kunnskapssenteret nr. 15 – 2015. ISBN 978-82-8121-966-3 ISSN 1890-1298.

31. Strøm V, Scheel I, Dalsbø TK, Kirkehei I. Effect of active labor market programs for immigrants. Rapport fra Kunnskapssenteret nr. 12 – 2015. ISBN 978-82-8121-962-5 ISSN 1890-1298.

32. Kurtze N, Nøkleby H, Berg RC. Effects of interventions in residential areas and neighbourhoods to promote social contact, social networks and social support. Rapport fra Kunnskapssenteret nr. 30 – 2015. ISBN 978-82-93479-05-5 ISSN 1890-1298.

33. Chalmers I, Nylenna M. A new network to promote evidence-based research. Lancet 2014; 384: 1903-4.

34. Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, Gøtzche PC, Lang T, for the CONSORT Group. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med 2001; 134: 663-94.

35. Armstrong R, Waters E, Moore L, Riggs E, Cuervo LG, Lumbignon P, Hawe P. Improving the reporting of public health intervention research: advancing TREND and CONSORT. J Public Health 2008; 30: 103-9.

36. von Elm E, Altman DG, Pocock SJ, Gøtzche PC, Vandenbroucke JP, for the STROBE initiative. Strengthening the reporting of observational studies in epidemiology (STOBE) statement: guidelines for reporting observational studies. BMJ 2007; 335: 806-8.

37. Whiting PF, Rutjes AWS, Westwood ME, Mallett S. Deeks JJ, Reitsma JB, Leeflang MMG, Sterne JAC, Bossuyt PMM, and the QUADAS2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011; 155: 529-36.

38. Brukermedvirkning i helseforskning i Norge. Forslag til retningslinjer og tiltak http://www.helse-nord.no/getfile.php/RHF%20INTER/Regionalt%20brukerutvalg/Regional%20brukerkonferanse/10022014__Rapport_Brukermedvirkning%20i%20helseforskning.pdf

39. Norderhaug IN, Lindahl AK, Mørland B, Jamtvedt G. Informasjon om forskningsbehov fra Kunnskapssenterets systematiske oversikter i 2010. Notat 2011. ISBN 978-82-8121-410-1.

Norwegian Institute of Public Health
June 2017
P.O. Box 4404 Nydalen
NO-0403 Oslo
Phone: +47 21 07 70 00

Norwegian Institute of Public Health