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World Health Organization

# MEDICAL DEVICES: MANAGING THE MISMATCH

An outcome of the Priority Medical Devices project

# Methodology briefing paper

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## Contents

This methodology paper was developed under the primary authorship of Josée Hansen with editing by Rhona MacDonald. The literature review was developed under the primary authorship of Warren Kaplan, with the help of Susan Mottram and colleagues at the Health Sciences Library, Leeds University. The scoping search was carried out by Hristina Petkova. Thanks are also due to Benjamin Schanker and Dima Samaha for providing valuable contributions in editing, writing, and research.

This publication was produced under the direction of Josée Hansen.

*The named authors alone are responsible for the views expressed in this publication.*

# Introduction

This briefing paper summarizes the methodology used by the *Priority Medical Devices (PMD)* project team for the research and subsequent content published in the report, *Medical Devices: Managing the Mismatch.* This briefing paper outlines the main steps undertaken by the *PMD* team and points to other sources of more detailed information regarding the methodology used (see the annexes of this paper and background papers 1 and 2).

## Background to PMD Project structure

The *PMD* project was established by WHO in 2007 with financial support from the Ministry of Health, Welfare and Sport of the Netherlands. The project was overseen by an Advisory Group of specialists in different areas of health care and medical devices. The writing of the report, *Medical devices: managing the mismatch* was supervised and reviewed by a Steering Group of medical devices specialists, expert clinicians, experts in regulation and renowned academics.

## Aims and Objectives of the PMD Project

The *PMD* project aimed at identifying gaps in the availability of medical devices and obstacles that might be hindering the full use of medical devices as public health tools. A second objective was the development of a methodology for identifying the medical devices needed to meet global public health needs. A third objective was to propose a possible research agenda for exploring how the gaps could be resolved and the obstacles removed.

As the project progressed, however, the following findings suggested that a change in the original objective of the project was necessary: 1) there are many medical devices available but not the most appropriate ones; 2) there are few gaps in the availability of medical devices on the market. These unanticipated findings prompted a project shift in focus to the many shortcomings related to medical devices. These problems, challenges, and failures amount to a mismatch, rather than a gap, that prevents medical devices from achieving their full public health potential.

# Methodologies used: purpose and rationale

Annex 1 describes in detail each step taken by the PMD team. The purpose and rationale for the methodologies used are outlined below.

## Taking a health needs approach to medical devices

A major objective of the *PMD* project was to develop an approach to choosing medical devices that is based, first and foremost, on the need for a positive health outcome. The *PMD* project team devised a stepwise approach to meeting public health needs. The first step in this approach identifies the most important public health problems. For the purposes of the *PMD* project, this meant mapping the high-burden diseases according to the *Global Burden of Disease (GBD) and Risk Factors*. The second step identifies how these health problems are best managed. To achieve this second step, the *PMD* project analysed relevant clinical guidelines. The third step links the results of the first two steps and produce a list of medical devices needed for the management of the identified high-burden diseases. This step involves identifying the category of medical devices and then identifying the specific models of devices required to perform the necessary procedures.

### In more detail

Following the mapping exercise to identify and map the high-burden diseases according to the *Global Burden of Disease (GBD) and Risk Factors,* the *PMD* project team selected relevant evidence-based clinical guidelines, developed to describe the management of 15 high-burden diseases, in order to identify the medical devices recommended for the management of a specific disease in clinical practice. Only clinical guidelines published after 2000 were included and selected separately for all 15 high-burden diseases and disabilities where the title referred to the disease or disability. WHO guidelines were selected, if possible. At the start of the project in 2007, WHO had developed guidelines for eight of the selected 15 high-burden diseases. For the purpose of the *PMD* project, medical devices were extracted from the clinical guidelines by two independent reviewers. Each reviewer independently scored the guidelines. Where interpretations differed, a specialist in the specific disease area was consulted who had the final word.

All medical devices (or techniques that involve medical devices) identified in the selected clinical guidelines were included in an "Availability Matrix" that formed the baseline of medical devices needed to manage the disease. Medical devices were categorized as preventive, diagnostic, therapeutic and assistive devices, according to the stages of health care. For these four subcategories, a distinction was made between medical devices for general use (e.g. stethoscope or thermometer) and disease-specific medical devices. More detailed information on the steps involved is available in Background paper 1.

The methodology used in this 3-step approach, and the subsequent findings, guided the content chosen to include in the report. However, some other methods were used by the *PMD* project team to provide a more contextual, in-depth, and qualitative analysis.

## Literature reviews

The *PMD* project team performed preliminary literature reviews to determine the extent to which information and outcomes of research on medical devices were publicly available. Then, an extensive literature review was conducted within the Ovid Medline, University of Leeds, and International Network of Agencies for Health Technology Assessment (INAHTA) database systems to evaluate past systematic reviews and meta analyses of clinical trials using medical devices for three of the high-burden diseases--cardiovascular disease, tuberculosis, and diabetes. The search strategy used for this literature review is described in Annex 2.

## Pilot surveys

Two pilot surveys were devised and validated, one for countries and one for specialists, to gather quantitative and qualitative information about medical device gaps. In addition, expert focus groups, round-table discussions and individual consultations helped to provide valuable qualitative information.

### Country surveys

Six countries were selected according to Human Development Index level. The questionnaire was sent to in-country WHO representatives who then forwarded the survey to the respective Ministry of Health and key health care-related associations in each selected country. The survey included questions around medical devices for three representative high-burden diseases: diabetes mellitus—an example of a noncommunicable disease; tuberculosis (TB) —an example of infectious disease; and road traffic accidents—an example of a condition for which early intervention could prevent long-term disability.

### Specialist surveys

This country survey was adapted to form a specialist questionnaire that contained medical device-related questions on each of 15 high-burden diseases. This questionnaire was sent directly to appropriate specialists in each of the high-burden diseases. The specialist survey was designed to help identify any clinical problems associated with the medical devices recommended for each high-burden medical condition. The selected specialists were also encouraged to suggest clinical areas that may require further medical device research.

## Purpose of the literature reviews and surveys

These specifically designed and validated questionnaires, combined with a comprehensive literature search and review, were used as the basis for identifying the evidence for, and experience of, medical device innovation, choosing and using

medical devices, and identification of the problems and challenges in these key areas, as well as possible ways of overcoming these barriers. Medical device activities were categorized in this way (i.e. medical device innovation and choosing and using medical devices) because these categories cover the processes and stages involved in the agenda to improve access to appropriate medical devices, and are directly or indirectly associated with the crucial 4 components—availability, accessibility, appropriateness, and affordability.

For a more detailed description of the pilot surveys, see Background paper 1.

## Areas of note

### Disability

Currently, no global burden of disability has been developed. Moreover, most clinical guidelines do not mention assistive products. In fact, the clinical guideline identified very few, if any, assistive products required to help functioning for those with the 15 high-burden diseases and disabilities. Therefore, to assess the assistive product gap, a different concept had to be used. The *PMD* project attempted to develop a linking methodological process that would help to identify assistive products needed by people with disabilities resulting from the selection of high-burden diseases. This process was complex and included a five step approach: 1) identification of 15 high-burden diseases by using the GBD; 2) description of ICD-10 and ICF as complementary systems; 3) bridging the GBD and ICF through core sets and functioning profiles; 4) delineating the ISO 9999; and 5) relating the ICF to the ISO 9999.

As a result, the project was able to bridge the 15 high-burden diseases to functions through ICF core sets. For those diseases where a core set did not exist, a functioning profile was developed. For a more detailed description of the methodology used, see Background paper 2.

## An exercise in reality

The *PMD* project team devised an exercise that could be used as a prompt to the areas that researchers, medical device choosers, and users should consider and apply to any of these key medical devices. However, it must be noted that this exercise is not an exact science. After having performed a needs assessment according to the stepwise approach (see above) and identifying the key medical devices involved, the following 4 questions could be applied.

1. Is this medical device currently available?
2. Is it currently accessible?
3. Is it currently appropriate to the specific context?
4. Is it affordable?

A negative answer to any of these questions requires further investigation that can be worked through to ascertain the main contributing factors to the negative answer. It is then possible to formulate a potential research framework for identifying clinical, technological, and/or process and systems knowledge-gaps to best improve access to appropriate medical devices and best address public health needs.

The answers to some of the 4 key questions may depend on local factors, but there are likely to be some common areas that can be more universally addressed, especially in low-income settings, such as the need for developing a more appropriate designs, appropriate staff training programmes, and manageable maintenance systems.

## The final methodology

One of the main objectives of the *PMD* project was to identify possible future areas of research which could help to improve access to appropriate medical devices. In order to do this, *PMD* project conducted a scoping search of the literature on recent or current research in the field of medical devices. The scoping search aimed to identify studies in the "pipeline" and to discover which medical devices are currently of scientific and developmental interest. Consistent with the overall methodology of this report, the scoping search was based on terms related to high-burden diseases and some cross-cutting themes (see annex 3 for the details of the search strategy for this scoping exercise).

To verify the findings from the scoping search, the *PMD* project team asked clinical experts from each of the 15 high-burden diseases to comment on the initial analysis. The *PMD* project team then drafted some possible areas of future research in each disease option which were reviewed by a second expert. These research areas are couched in terms of medical device availability, accessibility, appropriateness, and affordability.

# Methodology limitations

There are several limitations associated with the methodologies used by the *PMD* project.

- Using global burden of disease estimates as an indication of public health needs for medical devices produces research priorities pertinent more to global than to regional or national priorities.
- As ongoing research is included in the scoping exercise, there is no evidence yet that the results of this research will bring therapeutic benefits.
- Using management of specific diseases as a starting point for determining future research needs excludes research needed on medical devices for general use, such as hospital beds, sterilizers, and operating lamps.
- The proposed research areas represent the result of a highly selective process and therefore do not cover all possible relevant research areas.
- Assessing the need for research in specific areas calls for knowledge about current ongoing research. Yet, in the notoriously competitive environment of medical device development, information about their R&D is rarely publicly available.
- A constraining factor in the preparation of the suggested research agenda has been the paucity in the clinical guidelines consulted, of specific medical devices required for recommended health-care pathways.
- Research on tools for the prevention of ill-health and disability is a vital need but beyond the scope of the suggested research agenda.

# Conclusions

Despite the limitations of the methodologies used by the *PMD* project (as listed above), these methods were rationally chosen, robustly conducted, extensively reviewed, and have lead to pragmatic outcomes. The resources, background papers*, and reports developed from the *PMD* project will hopefully improve the use of medical devices, by facilitating their development and promoting their targeted use to address global health needs. But the work does not end here. As the report *Medical devices: managing the mismatch* shows, there is much more to be done to progress the access to appropriate medical devices agenda.

# List of background papers

Hansen J et al. *A stepwise approach to identify gaps in medical devices (Availability Matrix and survey methodology)* [Background paper 1 of the Priority Medical Devices project]. Geneva, World Health Organization 2010 (WH0/HSS/EHT/DIM/10.1). (http://whqlidoc.who.int/hq/2010/WHO_HSS_EHT_DIM_10.1_eng.pdf

Bougie T et al. *Building bridges between diseases, disabilities and assistive devices: linking the GBD, ICF and ISO 9999.* [Background paper 2 of the Priority Medical Devices project]. Geneva, World Health Organization 2010 (WH0/HSS/EHT/DIM/10.2). (http://whqlidoc.who.int/hq/2010/WHO_HSS_EHT_DIM_10.2_eng.pdf

Tice JA et al. *Clinical evidence for medical devices: regulatory processes focusing on Europe and the United States of America* [Background paper 3 of the Priority Medical Devices project]. Geneva, World Health Organization 2010 (WH0/HSS/EHT/DIM/10.3) (http://whqlidoc.who.int/hq/2010/WHO_HSS_EHT_DIM_10.3_eng.pdf

Dankelman J et al. *Increasing complexity of medical technology and consequences for training and outcome of care* [Background paper 4 of the Priority Medical Devices project]. Geneva, World Health Organization 2010 (WH0/HSS/EHT/DIM/10.4) (http://whqlidoc.who.int/hq/2010/WHO_HSS_EHT_DIM_10.4_eng.pdf

Beenkens F et al. *Context dependency of medical devices* [Background paper 5 of the Priority Medical Devices project]. Geneva, World Health Organization 2010 (WH0/HSS/EHT/DIM/10.5). (http://whqlidoc.who.int/hq/2010/WHO_HSS_EHT_DIM_10.5_eng.pdf

Petkova H et al. *Barriers to innovation in the field of medical devices.* [Background paper 6 of the Priority Medical Devices project]. Geneva, World Health Organization 2010 (WH0/HSS/EHT/DIM/10.6). (http://whqlidoc.who.int/hq/2010/WHO_HSS_EHT_DIM_10.6_eng.pdf

Carlson D et al. *Trends in medical technology and expected impact on public health.* [Background paper 7 of the Priority Medical Devices project]/ Geneva, World Health Organization 2010 (WH0/HSS/EHT/DIM/10.7). (http://whqlidoc.who.int/hq/2010/WHO_HSS_EHT_DIM_10.7_eng.pdf

Kaplan W et al. *Future public health needs: commonalities and differences between high- and low- resource settings* [Background paper 8 of the Priority Medical Devices project]. Geneva, World Health Organization 2010 (WH0/HSS/EHT/DIM/10.8). (http://whqlidoc.who.int/hq/2010/WHO_HSS_EHT_DIM_10.8_eng.pdf

# Annex 1: Summary of steps taken in the Priority Medical Devices project

| Process step | Justification / Goal / Procedure | Responsible Participants | Resulting Documents | Additional outcomes, remarks and conclusions |
|---|---|---|---|---|
| Set objectives | Develop objectives of the overall *Priority Medical Devices* project | Ministry of Health of the Netherlands<br><br>WHO | Project proposal | Formulated objectives:<br>* develop a methodology to identify gaps<br>* identify high priority medical devices<br>* identify cross-cutting themes<br>* identify possible barriers to medical device innovation<br>* propose a research agenda |
| Collect existing information on medical devices | Literature search to identify information on medical devices | Project team of health-care professionals, trainees, and consulted specialists | *Report assessment of available information in the public domain on medical devices.* Geneva, World Health Organization, 2007 (WHO/EHT/07.1). | No additional remarks |
| Identify public health priorities for the 15 high-burden diseases | In general, a similar approach as the one used for the *Priority Medicines* project was taken with the understanding that less data may be available for medical devices and that the subject matter may be more complex or broad; similar to medicines, medical devices can be prioritized according to burden of disease (diagnostic and therapeutic devices) | WHO<br><br>Advisory group meeting 2-3 July 2007 | Project proposal<br><br>Meeting report and list of participants | No additional remarks |
| Identify medical devices needed in the management of high-burden diseases | Literature search on three diseases (diabetes, TB and cardiovascular disease that would need many medical devices) | Dr Warren Kaplan, Boston University<br><br>Project team of health-care professionals, trainees, and consulted specialists | Annex 2 | Results indicated a general paucity of randomized controlled trials (RCTs) supporting clinical effectiveness of medical devices for the investigated disease. The exception of RCTs for drug eluting stents is noted.<br><br>The approach was changed from searching for clinical evidence to identifying medical devices through using the clinical guidelines. |
| Investigate existing clinical guidelines | A clinical perspective taken as the approach to identify the medical devices needed for health-care delivery in specified diseases or categories using:<br>1. WHO clinical guidelines<br>2. National Clearing House Guidelines (which refer to several other existing guidelines) | Project team of health-care professionals, trainees, and consulted specialists<br><br>Informal Consultations with specialists, 15-17 October 2008 | Hansen J et al. A stepwise approach to identify gaps in medical devices *(Availability Matrix and survey methodology)* [Background Paper 1 of the Priority Medical Devices project]. Geneva, World Health Organization 2010 (WHO/HSS/EHT/DIM/10.1). | Stepwise approach developed to identify medical devices needed in the management of high-burden diseases |
| Investigate clinical evidence of medical devices and relevant regulatory processes | Gather information on clinical evidence of medical devices and existing regulatory processes | Project team of health-care professionals, trainees, and consulted specialists<br><br>Dr Jeff Tice and Dr Mitch Feldmann, University of California; Dr Eric Mann, U.S. Food and Drug Administration (FDA); Dr Gert Bos, British Standards Institution (BSI); Dr Sabina Hoekstra, Ministry of Health, The Netherlands | Tice JA et al. *Clinical evidence for medical devices: regulatory processes focusing on Europe and the United States of America* [Background Paper 3 of the Priority Medical Devices project]. Geneva, World Health Organization 2010 (WHO/HSS/EHT/DIM/10.3). | Medical devices coming to the market are identified as safe for their intended use. Clinical outcomes are not part of the requirements for putting medical devices on the market. Post-market systems are not always performed as intended or desired. Assistive devices are not mentioned in clinical guidelines. |

| Process step | Justification / Goal / Procedure | Responsible Participants | Resulting Documents | Additional outcomes, remarks and conclusions |
|---|---|---|---|---|
| Link diseases, disabilities, and assistive devices | Develop a methodology to link high-burden diseases according to the global burdens of disease and disability to the International Classification of Functioning, Disability and Health (ICF), and to assistive devices according to ISO 9999 | Informal Consultations with specialists, 15-17 October 2008 | Bougie T et al. *Building bridges between diseases, disabilities and assistive devices: linking the GBD, ICF and ISO 9999* [Background Paper 2 of the Priority Medical Devices project]. Geneva, World Health Organization 2010 (WHO/HSS/EHT/DIM/10.2). | Developed lists of assistive products for use in treating functioning problems related to 15 high-burden diseases |
| Develop a methodology for identifying the gaps in availability and accessibility of medical devices: country survey | Develop surveys: web-based country survey on three diseases (diabetes, TB and road traffic injuries in six countries: low- and middle-income countries according to Human Development Index ) | Project team of health-care professionals, trainees, and consulted specialists<br><br>Dr Warren Kaplan, Boston University, Dr Hans Wener and Dr Annemiek Koster (methodologists)<br><br>Question Pro, developer of web based survey. | Survey<br>Hansen J et al. *A stepwise approach to identify gaps in medical devices (Availability Matrix and survey methodology)* [Background Paper 1 of the Priority Medical Devices project]. Geneva, World Health Organization 2010 (WHO/HSS/EHT/DIM/10.1). | Four out of six countries responded: response time was long and not all stakeholders responded |
| Develop a methodology for identifying the gaps in availability and accessibility of medical devices: specialist survey | Develop surveys: web-based specialist survey on 15 high-burden diseases (specialists were selected using,<br>1. WHO experts<br>2. International umbrella organizations<br>3. National umbrella organizations<br>4. Individual specialists | Project team of health-care professionals, trainees, and consulted specialists<br><br>Dr Warren Kaplan, Boston University, Dr Hans Wener and Dr Annemiek Koster (methodologists)<br><br>Question Pro, developer of web based survey. | Specialist survey.<br><br>Hansen J et al. *A stepwise approach to identify gaps in medical devices (Availability Matrix and survey methodology)* [Background Paper 1 of the Priority Medical Devices project]. Geneva, World Health Organization 2010 (WHO/HSS/EHT/DIM/10.1). | Response rate was 35%<br><br>Identified gaps: The specialist survey found that low-income settings have a dearth of technical information – for procurement, maintenance, repair and daily use. Gaps between the need and availability of devices were found to be greatest in low-income settings. A lack of assistive devices was indicated (except for wheelchairs and crutches).<br><br>The overall conclusion that emerged from these two surveys is that the survey methodology could be used in future surveys to identify gaps on use and availability of medical devices and related materials. |
| Address the concern of medical devices in use being dependant on their context | Take appropriateness of medical devices as a factor in the general accessibility and use of medical devices | Project team of health-care professionals, trainees, and consulted specialists<br><br>Advisory group members of the Dutch advisory group<br><br>Fernao Beenkens, Delft University, Dr Pieter Stolk, Top Institute Farma | Beenkens F et al. *Context dependency of medical devices* [Background Paper 5 of the Priority Medical Devices project]. Geneva, World Health Organization 2010 (WHO/HSS/EHT/DIM/10.5). | Availability is not the only important factor in regard to medical device use; information, context, and training are important factors. |
| Perform literature search on medical devices and relevant training | Education and training (with a consideration of the design of medical devices) are factored in the use of medical devices. | Dr Janny Dankelman, Delft University, the Netherlands; Prof Frank Painter, University of Connecticut | Dankelman J et al. *Increasing complexity of medical technology and consequences for training and outcome of care* [Background Paper 4 of the Priority Medical Devices project]. Geneva, World Health Organization 2010 (WHO/HSS/EHT/DIM/10.4). | No additional comments |

| Process step | Justification / Goal / Procedure | Responsible Participants | Resulting Documents | Additional outcomes, remarks and conclusions |
|---|---|---|---|---|
| Assess findings and develop conclusions up to this point | Availability (in terms of devices available on the market) is not the sole important factor. The appropriateness of medical devices for a given context are found to be a main barrier in accessibility, and a barrier to fully realizing the benefit of medical devices for their intended uses. | Project team of health-care professionals, trainees, and consulted specialists | Chapter 5 in the report, 'Medical Devices: Managing the Mismatch' | Worldwide sales in medical devices are found to be concentrated in the US, Europe and Japan. |
| Examine the barriers in medical device innovation and research | Address one of the initial objectives of the project: to identify the barriers to innovation in medical devices | Project team of health-care professionals, trainees, and consulted specialists<br><br>Dr Hristina Petkova, King's College, London | Petkova H et al. *Barriers to innovation in the field of medical devices* [Background Paper 6 of the Priority Medical Devices project]. Geneva, World Health Organization 2010 (WHO/HSS/EHT/DIM/10.6). | Innovation and uptake of medical technology are not a linear process but a convoluted path.<br><br>Research is concentrated for the use of high-resource countries, by high-resource countries, in high-resource countries. |
| Develop a fresh start: rather than speak of the gaps, we recognized that there is a mismatch between medical devices coming to the market and the proper application and implementation of all the new technologies in many settings. | Address one of the initial objectives of the project: to identify gaps | Project team of health-care professionals, trainees, and consulted specialists | Letter to the primary sponsor of the project (the Ministry of Health of the Netherlands). | The Ministry of Health of the Netherlands approved the new approach. |
| Consider the research in medical devices, necessary for managing current and future disease burden | Consider future disease and disability burdens to investigate future needs | Dr Warren Kaplan, Boston University | Kaplan W et al. *Future public health needs: commonalities and differences between high- and low-resource settings* [Background Paper 8 of the Priority Medical Devices project]. Geneva, World Health Organization 2010 (WHO/HSS/EHT/DIM/10.8). | There are commonalities in future disease burden between all WHO regions, including a shift from communicable diseases to more non-communicable diseases. An ageing population is found to be a worldwide trend. |
| Determine the technological trends | Medical devices are a dynamic field with constant developments. It was important to assess the impact that these developments might have on public health. | ECRI Institute, Philadelphia | Carlson D et al. *Trends in medical technology and expected impact on public health.* [Background Paper 7 of the Priority Medical Devices project]. Geneva, World Health Organization 2010 (WHO/HSS/EHT/DIM/10.7). | Technological trends can be linked to public health. |
| Develop potential research options and agendas moving forward | Address one of the initial objectives of the project: to propose a research agenda | Project team of health-care professionals, trainees, and consulted specialists<br><br>Dr Hristina Petkova, King's College, London.<br><br>Steering group | Chapter 6 in the report, 'Medical Devices: Managing the Mismatch' (methodology developed for consideration)<br><br>Annex 2 | A research agenda with targets for 18 high-burden diseases was developed, with consideration of trends and cross cutting themes. |
| Create a final report including all findings and conclusions | | | 'Medical Devices: Managing the Mismatch' | |

# Annex 2: Literature review of available clinical evidence for medical devices

## Introduction

Evidence-based medicine provides specific criteria for the collection and evaluation of results from clinical trials. The criteria have been developed for the assessment of methodological quality of clinical studies. Most of them were designed for assessment of the quality of randomized controlled trials (RCTs) only *(1)*.

One of the methods used in evidence-based medicine is the systematic review of literature. A systematic review is a comprehensive search for relevant reports on a specific topic, and those identified are then appraised and the results synthesized according to a predetermined and explicit method *(2)*. A meta-analysis is the statistical combination of at least two (and often several) studies to produce a single estimate of the effect of the examination under consideration. Variability in the methodological quality of studies included in these types of reviews, however, can lead to confusing results *(3, 4)*.

Clinical evidence of many medical devices is sparse or non-existent. Three kinds of literature review were conducted to confirm or refute this statement, and are discussed below:

1. Preliminary Ovid Medline (MEDLINE) search for systematic reviews and meta-analyses of procedures/device pairs for tuberculosis, diabetes and cardiovascular disease.
2. Focused literature search by the University of Leeds ("Leeds search") using several databases for an extremely common diagnostic medical device, the glucose-testing meter, also sometimes referred to as the blood glucose meter.
3. Search of the International Network of Agencies for Health Technology Assessment (INAHTA) online database in reference to the 15 high-burden diseases considered in the *PMD* project.

## MEDLINE search

The MEDLINE search was completed in March 2008: search terms were extracted from the Global Medical Device Nomenclature (GMDN) system and used in combination with the search term "device". In some cases, the GMDN-listed categories were logically split, or terms amended, to improve the accuracy of the search (e.g. the category "Anaesthetic and respiratory devices" was searched separately as "Anaesthetic" and "Respiratory" in regards to relevant devices). The results were grouped by total MEDLINE hits, MEDLINE hits limited to "review" and MEDLINE hits limited to "meta-analysis". This was done for three conditions: diabetes, tuberculosis and cardiovascular disease.

## Results of MEDLINE Global Medical Device Nomenclature (GMDN) Search

Results of the search are shown in Tables 2.1, 2.2 and 2.3, for diabetes, tuberculosis and cardiovascular disease, respectively. There was a paucity of hits for meta-analyses and reviews of clinical trials for diabetes and tuberculosis. For cardiovascular disease, there were many trials investigating clinical outcomes of drug-eluting stents (i.e. for restenosis or thrombosis). Other trials comparing therapeutic methods were also common (Tables 2.1–2.3).

## Leeds search

Susan Mottram and colleagues at the Health Sciences Library, Leeds University, performed a database search to identify three publication types on testing blood glucose levels in patients with diabetes:

- evaluation/comparative studies
- systematic reviews and meta analyses
- randomized controlled trials (RCTs).

Data published between 2000 and 2008 in Dutch, English, French, German and Spanish were assessed. The filters for the systematic reviews and RCT searches were based on those recommended by the Cochrane Collaboration and the Scottish Intercollegiate Guidelines Network (SIGN). The searches at Leeds University were designed to be sensitive rather than specific, and thus only a small percentage of results were relevant to the *PMD* project.

**Table 2.1. Results of the MEDLINE search for medical devices according to GMDN terms and diabetes**

| GMDN search terms | "Diabetes" | | |
|---|---|---|---|
| | Total MEDLINE hits | Hits including "review" | Hits including "meta-analysis" |
| Active implantable | 12 | 0 | 0 |
| Anaesthetic | 3 | 0 | 0 |
| Dental | 13 | 0 | 0 |
| Electro mechanical | 10 | 0 | 0 |
| Hospital hardware | 26 | 0 | 0 |
| In vitro diagnostic | 107 | 10 | 0 |
| Non-active implantable | 0 | 0 | 0 |
| Ophthalmic | 242 | 25 | 0 |
| Reusable | 8 | 0 | 0 |
| Single use | 430 | 37 | 1 |
| Assistive | 40 | 0 | 0 |
| Diagnostic | 3906 | 311 | 8 |
| Complementary therapy | 16 | 0 | 0 |
| Biologically derived | 1 | 0 | 0 |
| Healthcare facility | 18 | 0 | 0 |
| Laboratory equipment | 375 | 30 | 3 |
| Therapeutic | 5564 | 590 | 17 |
| Optical | 595 | 29 | 0 |
| Respiratory | 106 | 11 | 0 |

Table 2.2. Results of the MEDLINE search for medical devices according to GMDN terms and tuberculosis

| GMDN search terms | "Tuberculosis" | | |
|---|---|---|---|
| | Total MEDLINE hits | Hits including "review" | Hits including "meta-analysis" |
| Active implantable | 0 | 0 | 0 |
| Anaesthetic | 6 | 2 | 0 |
| Dental | 25 | 0 | 0 |
| Electro mechanical | 1 | 0 | 0 |
| Hospital hardware | 5 | 0 | 0 |
| In vitro diagnostic | 1168 | 1 | 0 |
| Non-active implantable | 0 | 0 | 0 |
| Ophthalmic | 10 | 0 | 0 |
| Reusable | 1 | 0 | 0 |
| Single use | 123 | 4 | 0 |
| Assistive | 1 | 0 | 0 |
| Diagnostic | 1222 | 59 | 3 |
| Complementary therapy | 303 | 14 | 0 |
| Biologically derived | 1 | 0 | 0 |
| Healthcare facility | 3808 | 95 | 0 |
| Laboratory equipment | 331 | 17 | 1 |
| Therapeutic | 631 | 52 | 0 |
| Optical | 145 | 9 | 0 |
| Respiratory | 384 | 29 | 0 |

Table 2.3. Results of the MEDLINE search for medical devices according to GMDN terms and cardiovascular disease

| GMDN search terms | "Cardiovascular disease" | | |
|---|---|---|---|
| | Total MEDLINE hits | Hits including "review" | Hits including "meta-analysis" |
| Active implantable | 212 | 18 | 0 |
| Anaesthetic | 977 | 68 | 2 |
| Dental | 468 | 60 | 1 |
| Electro mechanical | 124 | 13 | 0 |
| Hospital hardware | 187 | 1 | 0 |
| In vitro diagnostic | 1332 | 39 | 0 |
| Non-active implantable | 56 | 4 | 0 |
| Ophthalmic | 881 | 32 | 0 |
| Reusable | 24 | 2 | 0 |
| Single use | 6111 | 397 | 22 |
| Assistive | 192 | 26 | 3 |
| Diagnostic | 66333 | 5200 | 145 |
| Complementary therapy | 6232 | 29 | 1 |
| Biologically derived | 3 | 0 | 0 |
| Healthcare facility | 1611 | 115 | 0 |
| Laboratory equipment | 1608 | 169 | 8 |
| Therapeutic | 56023 | 6317 | 173 |
| Optical | 7495 | 544 | 3 |
| Respiratory | 1838 | 147 | 0 |

### Results of the search for "evaluation/comparative studies"

A total of 924 hits were reviewed, of which 114 (114/924 = 12.3%) were relevant to the *PMD* project (Table 3.1). The majority of the 114 studies enlisted fewer than 25 participants. There was one meta-analysis, two reviews and two comparative trials. The remainder were evaluation studies comparing devices: either device vs. device or device vs. a laboratory standard (Table 3.1). About one-third of the 114 studies evaluated new devices.

### Results of the search for "systematic reviews" and "randomized controlled trials"

The same database was searched using "randomized comparative trial", "trial" or "randomized" as the search terms for "glucose testing" or "glucose tolerance test". A total of 908 hits were reviewed, of which only 33 (33/903 = 3.6%) were relevant (Table 3.2).

The majority of these studies enlisted more than 25 participants, but only seven of the 33 were randomized, comparative trials. No meta-analyses and five reviews were found. Approximately one-fifth of the relevant studies were evaluations of new devices.

There was considerable overlap in the search results of this category and the others, but this has not been quantified.

Table 3.1 Evaluations and comparative studies for glucose-testing devices in patients with diabetes

| Type of study | Total number of studies | Number of studies with N>25 participants | Number of participants |
|---|---|---|---|
| Evaluation: single device vs. laboratory standard | 33 | 17 | 15–869 |
| Evaluation: two devices vs. laboratory standard | 5 | 4 | 114–286 |
| Evaluation: three devices vs. laboratory standard | 4 | 1 | 142 |
| Evaluation: four devices vs. laboratory standard | 3 | 1 | 110 |
| Evaluation: five devices vs. laboratory standard | 3 | 3 | 49–147 |
| Evaluation: >5 devices vs. laboratory standard | 2 | 1 | 107 |
| Evaluation: two or more devices vs. each other | 23 | 12 | 3–6010 |
| Evaluation: new device (pilot) | 30 | 2 | 1–154 |
| Evaluation: new device vs. laboratory standard | 4 | 0 | 4–23 |
| Meta-analyses | 1 | 0 | NA |
| Evaluation: randomized comparative trial | 2 | 2 | 109–202 |
| Reviews | 4 | NA | NA |
| Total | 114 | 43 | |

Note: NA= not available or not applicable

Table 3.2 Evaluations, clinical trials, randomized controlled trials and randomized comparative trials for glucose-testing devices in patients with diabetes

| Type of study | Total number of studies | Number of studies with N>25 participants | Number of participants |
|---|---|---|---|
| Evaluation: single device vs. laboratory standard | 8 | 3 | 12–4910 |
| Evaluation: two or more devices vs. laboratory standard | 2 | 1 | 100 |
| Evaluation: two or more devices vs. each other | 5 | 4 | NA |
| Evaluation: new device (pilot) | 6 | 5 | 27–323 |
| Meta-analyses | 0 | 0 | 0 |
| Evaluation: randomized comparative trial | 5 | 4 | 14–248 |
| Two or more devices: randomized comparative trial | 2 | 2 | 76–202 |
| Reviews | 5 | NA | NA |
| Total | 33 | 19 | |
| Meta-analyses | 1 | 0 | NA |
| Evaluation: randomized comparative trial | 2 | 2 | 109–202 |
| Reviews | 4 | NA | NA |
| Total | 114 | 43 | |

Note: NA= not available or not applicable

## The International Network of Agencies for Health Technology Assessment (INAHTA) search

The INAHTA database contains a series of publications known as health technology assessment (HTA) reports. All reports available as of January 2009 were reviewed in relation to 24 INAHTA-specified medical categories (Table 4.1).

The INAHTA classification scheme differs slightly from the 15 high-burden diseases according to the Global Burden of Disease (GBD) project *(5)*. Therefore, the categorization systems needed to be reconciled by mapping/assigning the relevant GBD high-burden diseases to each INAHTA category, as depicted in Table 4.1.

Each HTA citation was individually reviewed by looking at the title, abstract online and, if needed, the entire document. The reviewers assigned each HTA report a single GBD condition, though multiple conditions could apply to a particular HTA report. The GBD conditions 'HIV/AIDS' and 'malaria' found no corresponding HTA report.

Duplicates were defined as HTA reports found in more than one INAHTA-specified category. The number of duplicates is estimated at less than 10% the total number of reports.

Each HTA report was then assigned one of four mutually exclusive labels:

- "systematic review"
- "randomized controlled trial" (RCT)
- "cost-effectiveness study"
- "other" (i.e. report not appropriate for any of the above labels).

A further classification was done based on four mutually exclusive labels:

- "medical device"
- "procedure"
- "medicinal product (drug)"
- "other" (i.e. report not appropriate for any of the above labels).

HTA reports receiving an "other" label were considered irrelevant to the search. HTA reports were each assigned two labels, creating a matrix of 16 groups of which nine were relevant: "systematic review" ("device", "procedure", "drug"); "randomized controlled trial" ("device", "procedure", "drug"); and "cost-effectiveness study" ("device", "procedure", "drug").

## Results of the INAHTA search

Table 4.2 presents a summary of the search by INAHTA citation and the chosen groupings.

There were 1357 HTA reports in total. The vast majority (884/1357 = 65%) did not fall under one of the three groupings. The other 35% represented cost evaluations, systematic reviews and RCTs, respectively.

### Citations to high-burden disease according to GBD

Of the 1357 total HTA reports, 374 were

Table 4.1 Mapping INAHTA categories with GBD high-burden diseases

| Condition specified in the INAHTA database | GBD high-burden disease reviews under INAHTA classification |
|---|---|
| Cardiovascular disease | Cerebrovascular disease, ischaemic heart disease, road traffic accidents |
| Urologic male | None |
| Miscellaneous | Road traffic accidents, cerebrovascular disease |
| Transplant | Diabetes, road traffic accidents, cerebrovascular disease |
| Telemedicine | Cerebrovascular disease, ischaemic heart disease, unipolar depressive disorders, road traffic accidents, malignant neoplasms |
| Surgery procedures | Tuberculosis, COPD, malignant neoplasms, road traffic accidents, cerebrovascular disease |
| Oral | None |
| Skin connective tissue | Road traffic accidents, diabetes |
| Respiratory tract | COPD, malignant neoplasms, cerebrovascular disease |
| Psychiatry | Unipolar depressive disorders, road traffic accidents, malignant neoplasms |
| Ear nose throat | Hearing loss (adult onset) |
| Nutrition, metabolism | Diabetes, neonatal conditions |
| Nervous system | Cerebrovascular disease, road traffic accidents, unipolar depressive disorders |
| Diagnostic screening | Lower respiratory tract infections, malignant neoplasms, ischaemic heart disease, tuberculosis, neonatal conditions, unipolar depressive disorders, cataracts, road traffic accidents, hearing loss (adult onset), diabetes |
| Cancer | Malignant neoplasms |
| Musculoskeletal | None |
| Infectious disease | Diarrhoeal diseases, tuberculosis, road traffic accidents, neonatal conditions, malignant neoplasms, lower respiratory tract infections |
| Immunological | None |
| Blood, lymph | Malignant neoplasms, road traffic accidents |
| Pregnancy | None |
| Endocrine | Diabetes, cataracts |
| Eye | Cataracts, diabetes, neonatal conditions |
| Digestive | Malignant neoplasms |
| Congenital | Neonatal conditions |

COPD, chronic obstructive pulmonary disease.

Table 4.2. Summary of INAHTA citations and the search criteria

| INAHTA category citation | Number of hits | | | |
|---|---|---|---|---|
| | Systematic review | Randomized controlled trial (RCT) | Cost-effectiveness study | Other |
| Vascular | 15 | 7 | 32 | 63 |
| Miscellaneous | 13 | 3 | 7 | 60 |
| Urologic | 8 | 1 | 17 | 21 |
| Transplant | 5 | 0 | 2 | 10 |
| Telemedicine | 5 | 1 | 0 | 8 |
| Surgery | 14 | 4 | 10 | 58 |
| Oral | 1 | 0 | 3 | 7 |
| Skin | 7 | 3 | 6 | 11 |
| Respiratory | 6 | 1 | 0 | 20 |
| Psychiatric | 12 | 7 | 11 | 39 |
| Ear, nose, throat | 1 | 0 | 3 | 7 |
| Nutrition, metabolism | 6 | 0 | 9 | 23 |
| Nervous system | 6 | 2 | 13 | 26 |
| Diagnostic screen | 18 | 1 | 29 | 157 |
| Cancer | 12 | 2 | 26 | 106 |
| Musculoskeletal | 9 | 4 | 22 | 42 |
| Infectious disease | 5 | 0 | 22 | 42 |
| Immunological Disease | 1 | 0 | 5 | 4 |
| Blood, lymph | 1 | 0 | 6 | 14 |
| Pregnancy | 2 | 3 | 8 | 41 |
| Eye | 2 | 0 | 3 | 23 |
| Endocrine | 4 | 0 | 14 | 23 |
| Digestive | 11 | 1 | 14 | 41 |
| Congenital | 1 | 1 | 5 | 38 |
| Total | 165 | 41 | 267 | 884 |

Table 4.3 Summary of INAHTA reports as assigned to GBD high-burden diseases

| High-burden diseases | Number of INAHTA-database HTA reports assigned to high-burden diseases |
|---|---|
| Ischaemic heart disease | 115 |
| Malignant neoplasms* | 87 |
| Diabetes | 28 |
| Road traffic accidents | 24 |
| Cerebrovascular disease | 23 |
| Unipolar depressive disorders | 22 |
| Perinatal conditions | 17 |
| Neonatal conditions | 17 |
| Chronic obstructive pulmonary disease | 13 |
| Cataracts | 10 |
| Hearing loss, adult onset | 9 |
| Lower respiratory tract infections | 5 |
| Tuberculosis | 3 |
| Diarrhoeal diseases | 1 |
| Total | 374 |

* Lung, tracheal, bronchus and gastric cancers.

Table 4.4 Search terms from the INAHTA database mapped to high-burden diseases

| High-burden diseases | Systematic review | | | Randomized controlled trial (RCT) | | | Cost-effectiveness study | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Device | Procedure | Drug | Device | Procedure | Drug | Device | Procedure | Drug | Total |
| Road traffic accidents | 5 | 5 | 0 | 0 | 0 | 0 | 1 | 0 | 3 | 14 |
| Ischaemic heart disease | 4 | 7 | 0 | 0 | 1 | 2 | 11 | 11 | 0 | 36 |
| Cerebrovascular disease | 0 | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 3 |
| Diabetes | 1 | 6 | 0 | 0 | 0 | 0 | 1 | 3 | 2 | 13 |
| COPD | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 3 |
| Malignant neoplasms | 2 | 7 | 2 | 0 | 0 | 0 | 1 | 16 | 11 | 39 |
| Unipolar depressive disorders | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 3 |
| Hearing loss, adult onset | 1 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 3 |
| Lower respiratory tract infections | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 5 |
| Tuberculosis | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 3 |
| Cataracts | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Diarrhoeal diseases | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Perinatal conditions | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 2 | 0 | 3 |
| Total (%) | 14 (11%) | 35 (28%) | 2 (2%) | 1 (1%) | 2 (2%) | 2 (2%) | 16 (13%) | 35 (28%) | 20 (16%) | 127 |

COPD, chronic obstructive pulmonary disease.

assigned to high-burden diseases (Table 4.3). These 374 were evaluated further to categorize them in terms of one of the nine aforementioned labels. Approximately one-third of them were assigned a relevant label (127, or 34%); the remaining 247 reports were considered "other" and excluded. The data are summarized in Table 4.4.

Cost-effectiveness studies accounted for 57% of relevant studies and systematic reviews for 41%. RCTs constituted less than 5% of relevant studies. This number is misleading, however, as nearly every systematic review incorporated multiple RCTs.

## Limitations of the literature review

The most significant limitation of the INAHTA search came in assigning HTA reports to GBD categories. Each HTA report was assigned a GBD disease or condition based on its title and abstract. Following the methodology, the majority of INAHTA reports (72%) could not be assigned any high-burden disease.

Nomenclature was also a clear limitation of this analysis. The GBD nomenclature is different than that used in the HTA reports. In addition, the GBD categories differ from the INAHTA categories (Table 4.1), and the two classification systems had to be reconciled for the purposes of this review. It was challenging to assign the 15 high-burden diseases used by the *PMD* project to the INAHTA categories, and this could have been completed in alternate ways.

Moreover, some HTA references were not in English, and it was sometimes difficult to tell how many RCTs were used in systematic reviews. But even regardless of language, some papers did not break down their studies into such categories, which required subjective assignment to the appropriate category for the purposes of analysis. Furthermore, tables of included studies within the papers were often difficult to read or understand.

Regarding the Leeds search, one of the limitations was an overlap of information that was not quantified in the search for "systematic reviews" and "randomized controlled trials". Because of the nature of the search queries, the same study could be included in multiple categories if it included the different search terms. This suggests that the total number of studies found may be an overestimate, and that in reality the actual number of completed studies is lower. In addition, however, the nature of the search queries required a somewhat subjective assessment of relevance to the *PMD* project, which could have caused some studies to be excluded.

The MEDLINE search was limited to three specific diseases: diabetes, tuberculosis and cardiovascular disease; these were selected as representative high-burden diseases, and literature reviews for additional diseases or disease categories would be beneficial in future analyses. In addition, the MEDLINE search was limited by the selected GMDN terms used in search queries.

Like all literature reviews, the three searches (MEDLINE, Leeds, and INAHTA) included in this literature review depended on the quality of the selected databases. The inclusion or lack thereof in regards to relevant papers, and the proper referencing of keywords and titles rests within the constructs of the databases.

## Conclusions

The three literature reviews confirm a paucity of RCTs supporting evidence of efficacy and effectiveness of medical devices.

In the MEDLINE search, particularly, there was a nearly complete lack of meta-analyses of clinical trials for devices

associated with diabetes and tuberculosis. Searches identified many trials investigating clinical outcomes of drug-eluting stents (i.e. for restenosis or thrombosis) for cardiovascular disease; indeed, RCTs of this device category and disease predominate over all other diseases that were reviewed.

The Leeds search similarly indicated a general dearth of evidence, with a limited number of RCTs or randomized comparative trials, and most evaluation/comparative studies having consisted of fewer than 25 participants. Moreover, there was only one meta-analysis found for evaluation/comparative studies and no meta-analyses found for RCTs or randomized comparative trials within the database for blood glucose level testing.

Given the large number of HTA assessments in the INAHTA database, the relative lack of RCTs is striking, and further confirms the dearth of data on medical devices relevant to diabetes, tuberculosis and cardiovascular diseases. It is difficult to pinpoint the precise number of RCTs related to medical devices found in this dataset, due to the fact that many of the identified systematic reviews included them as well.

The difficulty encountered in this review when trying to reconcile various nomenclatures suggests that these databases may benefit by the development of a standard disease classification system.

Ultimately, the literature review indicated a significant lack of data and literature in regards to medical devices for many diseases, and additional research is needed to further understand the landscape of medical devices and promote future development.

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# Annex 3: Scoping search for the research agenda

In order to inform the research agenda, a scoping search was performed regarding the available literature on recent or current research in the field of medical devices. The scoping search aimed to identify studies in the "pipeline" and to capture which medical devices are currently of scientific and developmental interest. The emphasis was on searching for publications on studies published from the year 2000 up until the 25 March 2010. Consistent with the overall methodology of this report, the scoping search was based on search terms relating to high-burden diseases and some cross-cutting themes. Ovid Medline was used as the main medical database, and the search strategy is presented in the table below. The terms are grouped as follows:

- "Device" terms
- "Research" terms
- "Device" AND "Research" (combined search)
- "Developing country" terms
- "Developed country" terms
- Disease terms:
  - "Cancer"
  - "Cataract"
  - "Cerebrovascular disease"
  - "COPD"
  - "Diabetes"
  - "Hearing loss"
  - "HIV/AIDS"
  - "Ischaemic heart disease"
  - "Lower respiratory tract infections"
  - "Malaria"
  - "Perinatal conditions"
  - "Road traffic injuries"
  - "Tuberculosis"
  - "Unipolar depressive disorder"
- Research in devices AND Disease terms AND Country setting (combined search for each individual condition in terms of current research in medical devices in developing and in developed countries.

Overall, the scoping search showed a very low number of studies in medical devices relevant to high-burden diseases, both for developed and for developing countries. It became clear that cancer and HIV/AIDS are the disease areas where most research occurs or is published in the field of medical devices (search numbers(s) 39 and 40; 51 and 52, respectively [see table below]). There are 11 identified studies related to perinatal conditions. However, for the majority of the diseases we searched, there appears to be very limited existing research on medical devices, as the number of publications was often below 10 for each disease. Moreover, not all publications found in the searches are relevant to medical devices.

This search was scoping in nature, and not a systematic literature review. However, the findings did indicate considerable gaps in the existing literature on medical device research for high-burden conditions, and that this scoping search could be the basis of a future systematic literature review.

To verify the findings of the scoping search, specialists from each of the high-burden diseases were asked to comment on the analyses of research priorities and the identified gaps. The specialists commented on the research options and provided specific input.

Searches 39 - 66 in the table indicate the final combined search, showing the number of papers, generated for the specified search criteria. The delimiter 'and' is used to identify those papers which include all search criteria as mentioned in the left-hand side column of the table.

### Scoping search using Ovid Medline (last updated on 25 March 2010)

| | | | |
|---|---|---|---|
| "Device" terms | 1 | (medical adj* (devic* or technolog* or innovation* or tool* or equipment* or applianc*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] | 22174 |
| "Research" terms | 2 | (research or stud* or investigat* or explor* or examin*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] | 10034480 |
| "Device" AND "Research" | 3 | 1 and 2 | 9750 |
| | 4 | (countr* or setting* or nation* or state*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] | 1893045 |
| | 5 | exp Developing Countries/ | 53207 |
| | 6 | (developing or low resource* or low income or low funded or under funded or poor or third world).mp. | 509371 |
| | 7 | 4 and 6 | 145569 |
| "Developing country" terms | 8 | 5 or 7 | 145569 |
| | 9 | (developed or high resource* or high income or high funded or over funded or rich or wealth* or affluen*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] | 884172 |
| | 10 | exp Developed Countries/ | 26084 |
| | 11 | 4 and 9 | 139048 |

| | | | |
|---|---|---|---|
| "Developed country" | 12 | 10 or 11 | 147476 |
| | 13 | exp Neoplasms/ or malignant neoplasm:.mp. | 2096033 |
| | 14 | (cancer or oncolog* or malignan* or tum?r or neoplasm*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] | 2195198 |
| Cancer terms | 15 | 13 or 14 | 2477971 |
| "Cataract" | 16 | exp Cataract Extraction/ or exp Cataract/ or cataract$.mp. | 47265 |
| "Cerebrovascular disease" | 17 | exp Stroke/ or exp Cerebrovascular Disorders/ or Cerebrovascular disease.mp. or *Cerebral Hemorrhage/ or *Brain Ischemia/ | 222013 |
| | 18 | Chronic obstructive pulmonary disease.mp. or exp Pulmonary Disease, Chronic Obstructive/ | 23067 |
| | 19 | COPD.mp. | 15709 |
| "COPD" | 20 | 18 or 19 | 25896 |
| "Diabetes" | 21 | diabetes.mp. or exp Diabetes Mellitus/ | 322654 |
| "Hearing loss" | 22 | hearing loss.mp. or exp Hearing Loss/ | 52510 |
| | 23 | HIV.mp. or exp HIV/ | 206301 |
| | 24 | AIDS.mp. or exp Acquired Immunodeficiency Syndrome/ | 153889 |
| HIV/AIDS | 25 | 23 or 24 | 281451 |
| | 26 | exp Coronary Disease/ or Ischaemic heart disease.mp. | 160327 |
| | 27 | isch?mic heart disease.mp. | 16643 |
| "Ischaemic heart disease" | 28 | 26 or 27 | 169630 |
| "Lower respiratory tract infections" | 29 | exp Respiratory Tract Infections/ or *Pneumonia/ or Lower respiratory infection*.mp. or *Bronchitis/ | 243710 |
| "Malaria" | 30 | malaria.mp. or exp Malaria/ | 50917 |
| "Perinatal conditions" | 31 | *Infant Mortality/ or *Pregnancy Complications/ or *Infant, Newborn/ or *Infant, Premature/ or Perinatal condition*.mp. or *Infant, Low Birth Weight/ | 103942 |
| | 32 | *"Wounds and Injuries"/ or exp Accidents, Traffic/ or road traffic.mp. | 63563 |
| | 33 | road traffic injuries.mp. | 271 |
| | 34 | road traffic injury.mp. | 89 |
| Road traffic injuries" | 35 | 32 or 33 or 34 | 63563 |
| TB | 36 | exp Tuberculosis/ or tuberculos*.mp. | 163405 |
| "Unipolar depressive disorder" | 37 | exp Depressive Disorder/ or unipolar depressive disorder*.mp. | 63955 |
| Research in devices AND Cancer | 38 | 3 and 15 | 649 |
| Research in devices AND Developing countries AND Cancer | 39 | 3 and 8 and 15 | 38 |
| Research in devices AND Developed countries AND Cancer | 40 | 3 and 12 and 15 | 40 |
| Research in devices AND Developing countries AND cataract | 41 | 3 and 8 and 16 | 0 |
| Research in devices AND Developed countries AND cataract | 42 | 3 and 12 and 16 | 1 |
| Research in devices AND Developing countries AND Cerebrovascular disease | 43 | 3 and 8 and 17 | 1 |
| Research in devices AND Developed countries AND Cerebrovascular disease | 44 | 3 and 12 and 17 | 3 |
| Research in devices AND Developing countries AND COPD | 45 | 3 and 8 and 20 | 0 |
| Research in devices AND Developed countries AND COPD | 46 | 3 and 12 and 20 | 1 |
| Research in devices AND Developing countries AND Diabetes | 47 | 3 and 8 and 21 | 5 |
| Research in devices AND Developed countries AND Diabetes | 48 | 3 and 12 and 21 | 6 |
| Research in devices AND Developing countries AND hearing loss | 49 | 3 and 8 and 22 | 1 |
| Research in devices AND Developed countries AND hearing loss | 50 | 3 and 12 and 22 | 2 |
| Research in devices AND Developing countries AND HIV/AIDS | 51 | 3 and 8 and 25 | 25 |
| Research in devices AND Developed countries AND HIV/AIDS | 52 | 3 and 12 and 25 | 16 |
| Research in devices AND Developing countries AND Ischaemic heart disease | 53 | 3 and 8 and 28 | 0 |
| Research in devices AND Developed countries AND Ischaemic heart disease | 54 | 3 and 12 and 28 | 1 |
| Research in devices AND Developing countries AND Lower respiratory tract infections | 55 | 3 and 8 and 29 | 4 |

| | | | |
|---|---|---|---|
| Research in devices AND Developed countries AND Lower respiratory tract infections | 56 | 3 and 12 and 29 | 2 |
| Research in devices AND Developing countries AND Malaria | 57 | 3 and 8 and 30 | 3 |
| Research in devices AND Developed countries AND Malaria | 58 | 3 and 12 and 30 | 3 |
| Research in devices AND Developing countries AND Perinatal conditions | 59 | 3 and 8 and 31 | 11 |
| Research in devices AND Developed countries AND Perinatal conditions | 60 | 3 and 12 and 31 | 4 |
| Research in devices AND Developing countries AND Road traffic injuries | 61 | 3 and 8 and 35 | 0 |
| Research in devices AND Developed countries AND Road traffic injuries | 62 | 3 and 12 and 35 | 6 |
| Research in devices AND Developing countries AND TB | 63 | 3 and 8 and 36 | 7 |
| Research in devices AND Developed countries AND TB | 64 | 3 and 12 and 36 | 7 |
| Research in devices AND Developing countries AND Unipolar Depressive Disorder | 65 | 3 and 8 and 37 | 0 |
| Research in devices AND Developed countries AND Unipolar Depressive Disorder | 66 | 3 and 12 and 37 | 0 |